Cancer-Induced Bone Pain (CIBP): Clinical Characterisation and Biomarker Development

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Contents

Declaration

I, Angela Clare Scott (nee Boyd), hereby declare that I have completed this thesis.

I conducted the literature review in Chapters 2 to 4.

The data collection in Chapter 5 was completed by Sandra McConnell and Siobhan Duncan. I subsequently collated the results in a database and conducted the statistical analysis with support from Cat Graham.

For the research described in Chapters 6 to 9, I wrote the protocol, consent form and patient information sheets, and submitted the study to the ethics and R&D departments. All patient assessments and data collection were undertaken by me. I arranged the data into a database and analysed the results. Additional statistical analysis was provided by Professor Gordon Murray.

This work has not been submitted for any other degree or professional qualification.

Signed:

Date: 15 April 2010

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Abstract

Background: Cancer-induced bone pain (CIBP) is a major clinical problem and a considerable therapeutic challenge. Radiotherapy (XRT) is the gold standard treatment for CIBP, but only half of patients achieve adequate analgesia. Patients have increased morbidity, anxiety and depression and reduced performance and quality of life. Despite these issues, CIBP is a neglected area of clinical research. Animal models have increased current knowledge of the pathophysiology, but clinical research is needed to translate these findings from bench to bedside. Also lacking is a standardised, comprehensive tool to assess CIBP and clinical biomarkers to predict analgesic response to treatment.

Aims:

1) To summarise current understanding of the pathophysiology, epidemiology, clinical features, assessment and management of malignant bone disease and CIBP.

2) To characterise CIBP using quantitative sensory testing as a measure of altered sensory processing.

3) To establish systematically the sensory, cognitive, affective and functional components of CIBP to develop a comprehensive assessment tool.

4) To explore whether clinical biomarkers can be developed to aid prediction of response to treatment for CIBP, in particular XRT.

Results: Assessment of CIBP, characterising the multi-dimensional components, was clinically practical and acceptable to patients. Using objective measures of function, patients with CIBP were a frailer, less active population compared with healthy adults. Prior to treatment, pain was severe with relationships seen between CIBP and sensation, mood, fear avoidance, catastrophizing and function. Patients who dropped out prior to follow up were significantly less active, with higher levels of depression and fear avoidance behaviour. Sixty-nine percent of evaluable patients who completed two assessments (48% of all patients on an intention-to-treat basis), achieved an analgesic response to XRT for CIBP, as defined as an improvement of $\geq$ 30% in the Brief Pain Inventory worst pain score two months after treatment. All dimensions of pain, fear avoidance and catastrophizing improved significantly in responders, but not non-responders. Anxiety, depression and emotional distress fell by a greater degree in responders. No objective functional differences were seen after XRT. Clear evidence of altered sensory processing was seen at the site of CIBP with abnormalities in both mechanical and thermal parameters. XRT resulted in alterations in response to evoked stimuli in responders with a greater number of patients in whom sensation normalised after XRT compared with non-responders. Patients with a combination of altered sensation to thermal, pin prick and wind up stimuli showed the largest reduction in worst pain after XRT. Abnormal cool sensation at the site of CIBP was an independent predictor of analgesic response to treatment.

Conclusion: Strong associations exist between CIBP, sensation, cognition, mood and function. Multi-dimensional assessment should be performed to improve quality of life. Translational research to provide targeted individualised treatment should be high on the research agenda. Future work should focus on thermal sensory processing as a potential clinical biomarker of response to palliative XRT for CIBP.

Chapter 1 INTRODUCTION

Cancer pain is common and distressing, but fortunately is potentially controllable in approximately 80% of patients utilising appropriate guidelines to aid pain management (1). However, studies have shown that pain is often inadequately treated in cancer (2). This is of concern as it is estimated that up to 70% of patients with advanced malignancy experience significant pain (3). Reasons for poor pain control in this setting have been examined. The Eastern Cooperative Oncology Group (ECOG) conducted a large, group-wide survey to determine physicians' attitudes and practice in cancer pain management (4). Eighty-six percent of responders felt that the majority of patients with pain were under medicated. Factors identified as reasons for inadequate pain management included patient reluctance to report pain and to take analgesics, concerns regarding side effect management and tolerance, inadequate use of adjuvants, and physician reluctance to prescribe opioids. The study also identified that 31% of physicians would wait until the patient's prognosis was six months or less before choosing maximal analgesia. However, poor pain assessment was felt to be the most important barrier to adequate pain control. Lack of a standard pain assessment tool was a crucial component.

Cancer-induced bone pain (CIBP) is a major clinical problem. Breast, prostate and lung cancer are common and are also most likely to develop debilitating symptomatic bony metastases. As well as pain control issues, there are also concerns regarding pathological fracture and spinal cord compression. Up to 85% of patients with CIBP have increased morbidity, reduced performance, increased anxiety and depression and reduced quality of life. In a study of 157 oncology outpatients with pain from bony metastases, the most important factors that predicted quality of life were depression, social functioning and physical functioning (5). Studies suggest, that like other causes of cancer pain, CIBP is often under treated (6). The pain may also be disproportionate to the size or degree of bone involvement.

CIBP remains a considerable therapeutic challenge because it is a complex pain syndrome. It involves a background pain (that often responds to opioid medication), spontaneous breakthrough pain and movement-related pain, which can restrict patients significantly. Spontaneous breakthrough pain and movement-related pain can be particularly difficult to treat without unacceptable side effects. More than 50% of patients with CIBP have troublesome opioid side effects. Current analgesic therapy is also not targeted towards the specific underlying mechanism in the nervous system. Radiotherapy (XRT) is the current standard treatment for CIBP, although only 55% of patients will achieve adequate analgesia from palliative XRT (7, 8), and it can take up to six weeks to work. Other options for treatment include chemotherapy, hormonal therapy, radioisotopes, surgery and bisphosphonates. However, these interventions may also take weeks to provide symptomatic benefit. Therefore, adequate analgesia to complement these treatments is required to ensure maximal pain relief at the different points in each patient's illness.

CIBP is a neglected area of clinical research. Firstly, the underlying pathophysiology of bone pain is not understood fully. There is a clear need for increased understanding of the mechanisms in order that novel, effective treatments can be developed and the management of this challenging problem can be improved. By linking symptoms with mechanisms we may develop treatment that can focus on the most distressing symptoms. Also lacking in this field is research to develop a standardised, comprehensive tool to assess CIBP and the consequences of treatment. Lastly, research into CIBP has not focused adequately on targeted, personalised treatment. There is a need for trials exploring the development of clinical biomarkers to predict analgesic response to treatment for CIBP, such as XRT. Being able to provide individualised treatment potentially has both personal and health economic rewards.

The aims of the research presented in this thesis are:

1. To summarise current understanding of the pathophysiology, epidemiology, clinical features, assessment and management of malignant bone disease and CIBP.
2. To characterise CIBP using quantitative sensory testing (QST) as a measure of altered sensory processing.

3. To establish systematically the sensory, cognitive, affective and functional components of CIBP to develop a comprehensive assessment tool.
4. To explore whether clinical biomarkers can be developed to aid prediction of response to treatment for CIBP, in particular XRT.

The intention of this research is to increase the knowledge and understanding of CIBP to allow selection of the most appropriate treatment for the patient, targeted to help their specific needs. In the future this form of assessment may be extended to other chronic pain syndromes.

The next few chapters will explore in detail the current understanding and available literature on CIBP. Subsequent chapters will describe the individual studies undertaken and recommendations (Table 1).

Table 1. Summary of Trials

Chapter	***Description of Study***	
5	Pilot Study 1	Characterisation of CIBP prior to XRT (n=17).
	Pilot Study 2	Assessment of CIBP before and after XRT (n=28)
	Data from the two pilot studies was combined to identify the mechanisms of CIBP using sensory testing (n=45).	
	Analysis of patients from pilot study 2 able to complete an assessment after XRT (n=23).	
The results presented in Chapters 6-9 are from a single study of patients with CIBP.		
6	Clinical characterisation of the cognitive, affective, sensory and functional components of CIBP prior to treatment (n=60).	
7	Response to palliative XRT at 6-8 weeks after treatment (n=42).	
8	Comparison of responders and non-responders to XRT (n=42).	
9	Assessment of CIBP at 3-4 months after XRT (n=28).	

For the literature review, MEDLINE (1950-2009) was searched electronically. The keywords incorporated MeSH terms, all subheadings were included and "*" was used for truncation. The results were limited to English language journals and studies involving humans except for searching for literature relating to animal models of CIBP. The following search terms were used in various combinations (e.g. Cancer AND Bone AND Pain):

- Cancer
- Bone
- Pain
- Metastases
- Epidemiology
- Pathophysiology
- Allodynia
- Hyperalgesia
- Sensitisation
- Breakthrough
- Hypercalcaemia
- Fracture
- Spinal Cord Compression
- Analgesia
- Paracetamol
- Anti-inflammatory
- Opioid
- Adjuvant
- Bisphosphonate
- Radiotherapy
- Chemotherapy
- Radioisotope
- Assessment
- Mood
- Anxiety
- Depression
- Distress
- Visual Analogue Scale
- Numerical Rating Scale
- Brief Pain Inventory
- McGill Pain Questionnaire
- Hospital Anxiety and Depression Scale
- Fear and Avoidance of Pain Scale
- Fear
- Avoidance
- Pain Catastrophizing Scale
- Catastrophizing
- Quantitative Sensory Testing
- Thermal
- Function
- GAITRite
- activPAL
- Physical Activity
- Performance Status
- Predictor
- Biomarker

Chapter 2 BACKGROUND

2.1 *Pain*

As human beings we are programmed to react to pain as a protective mechanism. It is indispensable for survival. From a medical perspective, it has a number of definitions. In 1968 McCaffery described pain as "what the person says it is and exists whenever he or she says it does" (9). It was defined by the International Association for the Study of Pain (IASP) Subcommittee on Taxonomy in 1986: pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (10). These definitions are relatively recent, but pain has been of major medical interest for centuries. It may be a source of great disability with an impact on quality of life, and unfortunately it may be poorly treated. It is a frequent occurrence in everyday life and has numerous guises: pain may be acute or chronic due to both malignant and non-malignant causes. Fortunately, advances have allowed further classification of pain into pain syndromes enabling the development of frameworks for diagnosis and treatment.

2.2 *Cancer Pain*

Cancer is common. Recent figures show that in 2006, there were an estimated 3.2 million cancer cases (excluding non-melanoma skin cancer) diagnosed in Europe and 1.7 million deaths from cancer (11). Even if age-specific cancer mortality rates remain constant, an increase in absolute numbers of cancer cases and deaths is likely in the future due to the expanding elderly population. The burden of cancer will rise. According to current statistics, approximately one in three of us will at some point in our life develop cancer (12). Both the disease and its treatment may result in various clinical problems, but cancer pain is one of the most frequent symptoms associated with malignancy. It is often the symptom that patients and the general public fear the most. It is a common belief that pain and cancer are strongly linked. In a study of 496 members of the public, it was found that cancer was perceived as an extremely painful disease relative to other medical conditions. Pain resulting from both cancer and treatment were significant concerns for nearly half of respondents, and 57% thought cancer patients die a painful death (13).

Cancer pain or cancer-related pain distinguishes pain experienced by cancer patients from that experienced by patients without cancer. Pain affects approximately half of patients with a new diagnosis of cancer, approximately a third of those undergoing treatment, and three quarters of those with advanced disease, resulting in significant distress and morbidity (14, 15). Different types of pain occur in cancer patients. It is important to distinguish between acute and chronic pain, predictable and unpredictable pain and the cause of the pain which may be due to the tumour itself, anti-cancer or other treatment, cancer-related debility or some unrelated cause, such as concurrent disease. Many patients have multiple pains (15). In a survey, 30% had only one site of pain, 39% had two sites and 31% had three or more sites. The main cause of pain was the cancer itself in 85% of patients. Seventeen percent had pain attributable to anti-cancer treatment, 9% had pain due to cancer-related debility and in 9% the pain was secondary to another non-malignant disease (16). As well as varying with stage of disease, the prevalence of cancer pain varies depending on the primary tumour site. For example, in patients with oesophageal, prostate and head and neck tumours, pain is far more prevalent than in leukaemia (17, 18). Variable prevalence of cancer pain depending on tumour type was also demonstrated by Daut and Cleeland (19). In addition, they showed that pain, when present, is often of at least moderate intensity and is felt to interfere with patients' activity and enjoyment of life to a moderate to severe degree.

According to the underlying pathophysiology, cancer pain can also be classified into a particular type: nociceptive and neuropathic pain (18). Addressing the basic mechanism may have important therapeutic implications. Nociceptive pain is a consequence of tissue injury to somatic or visceral structures and results from activation of peripheral nerve fibres sensitive to noxious stimuli. Neuropathic pain results from nerve compression or injury in the peripheral or central nervous system and results in pain of a different nature. When classified this way, a pain survey showed that of the 4542 pains in 2266 patients, pain was of nociceptive origin in 76% (25% somatic bone, 29% somatic soft tissue, 22% visceral), neuropathic in 20% and unknown in 4% (16). The mechanisms underlying both nociceptive and neuropathic pain are described later in the chapter. Advances have also allowed further classification of pain into pain syndromes, enabling the development of frameworks for diagnosis and treatment (18). Examples include brachial or lumbosacral plexopathy and pancreatic pain. Pattern recognition with careful evaluation allows us to identify these syndromes. This has significant clinical utility and aids subsequent clinical decision making.

However, cancer pain is more than simply the physical pain. It is viewed as a multi-dimensional construct, encompassing not only the physiological and sensory components, but also affective, behavioural and cognitive aspects (20). Thus, effective management of cancer pain involves understanding of the pathophysiology of the pain, appropriate evaluation, delivery of appropriate analgesics and interventions and the ability to address other associated issues, such as psychological, social, cultural, spiritual and religious factors. However, despite advances in the treatment of cancer pain, it continues to be of major concern to patients and health professionals, as well as the wider community.

One such problem is pain due to malignant bone disease, referred to as **Cancer-Induced Bone Pain (CIBP),** and this particular syndrome is the focus of this thesis.

2.3 Metastatic Bone Disease & CIBP: Epidemiology

Bone pain may occur as a consequence of a primary bone tumour, but far more frequently it is due to metastatic malignancy. Metastatic cancer invades bone in 60-84% of cases (8, 21). Bone is the third most common site for metastatic disease, but is the most common site of pain (8). Bone metastases are most often seen in breast, prostate, lung, thyroid and renal cancers and myeloma. In view of the frequency of breast and prostate cancer in the population and the predisposition for bony spread, 70% of these patients have evidence of bone metastases at post-mortem (22). It is more difficult to estimate accurately the frequency of bone metastases prior to death, as assessments depend on the sensitivity of the diagnostic test. Bone metastases can potentially be found at any bony site, but due to the nature of haematogenous spread, in particular via the venous plexus, the axial skeleton and proximal long bones are most commonly affected (22). This includes the vertebrae, pelvis, ribs, femora and skull, with lumbar vertebrae being the most common site (23). Different primary tumours do not tend to show a significant difference in their distribution in the skeleton, except for prostate, bladder, cervical and rectal cancers which often involve the pelvis. A solitary bone metastass is not common, but if it does occur, it is usually secondary to either renal cancer or neuroblastoma (24).

Varying pathophysiological mechanisms lead to differing radiological appearances of bone metastases. As a result, they are referred to as lytic, sclerotic or mixed lesions. Lytic metastases are seen most commonly in myeloma, breast, lung, thyroid and renal cancers. They occur when bone resorption and destruction predominate. Sclerotic lesions are found when osteoblastic activity prevails and are typical of prostate cancer metastases. In some malignancies, such as breast cancer, both types of process are found. The mechanisms of development of these lesions are discussed below.

Although most patients with widespread malignancy have a poor prognosis, survival varies and in cancers such as breast and prostate this may stretch into years. This is in part due to the expanding range of available anti-neoplastic agents. Median survival ranges from 20 months with first recurrence of breast cancer, up to 53 months in good performance status men with bone only prostate cancer, 2 to 3 years in myeloma, but only 3 to 6 months with lung cancer. Thus, due to their longer clinical course and high incidence, breast and prostate cancer patients account for 80% of those with metastatic bone disease (25). However, co-existing visceral disease is very important in determining prognostic differences between patients with bony disease from the same primary tumour (22). Other well-established prognostic factors in metastatic bone disease include disease-free interval, performance status, oestrogen receptor status, age and histological grade in breast cancer, skeletal distribution, alkaline phosphatase, haemoglobin and prostate specific antigen (PSA) fall in prostate cancer, and factors such as β2-microglobulin, C-reactive protein (CRP), immunologic phenotype, lactate dehydrogenase (LDH), serum creatinine and hypercalcaemia in myeloma (21, 25).

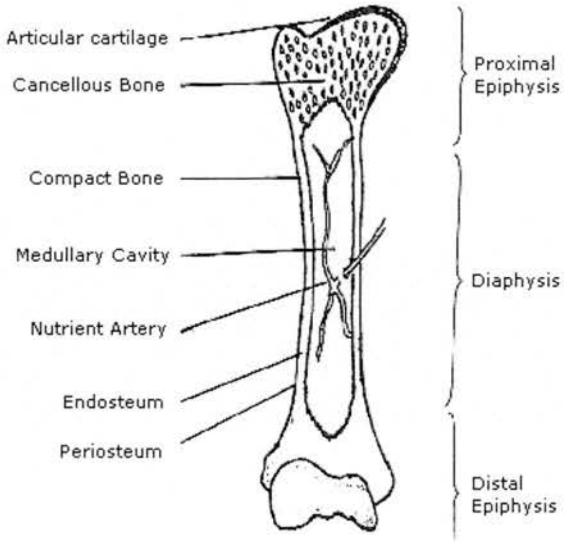
2.4 Pathophysiological Mechanisms

The pathophysiological mechanisms of CIBP are not fully understood, but have been explored both in animal and clinical studies to aid future management of the problem. However, it is useful firstly to explore the anatomy and physiology of bone, mechanisms of bone metastases and basic pain pathways. In order to develop rational assessment tools and therapies, it is necessary to understand the various processes involved.

2.4.1 Anatomy & Physiology of Bone

The adult human body comprises 206 bones and these make up about 18% of the weight of the human body (26). In the adult, bones are grouped into two main divisions: the axial skeleton which comprises the skull, hyoid, auditory ossicles, vertebral column and thorax, and the appendicular skeleton which comprises the upper and lower limbs, and the pectoral and pelvic girdles. Almost all the bones can be classified into five types depending on their shape: long, short, flat, irregular and sesamoid. Macroscopic structure of bone is best considered with a typical long bone such as the humerus. The diaphysis is the long shaft or body of the bone, with the epiphyses at either end. The metaphyses join the diaphysis to each epiphysis in mature bone. Each epiphysis is covered by a layer of articular cartilage where it forms a joint with other bones. The other areas of bone not covered by articular cartilage are encased with a dense connective tissue known as the periosteum. The medullary cavity is the space within the diaphysis which contains the bone marrow and lining this cavity is the endosteum (26) (Figure 1).

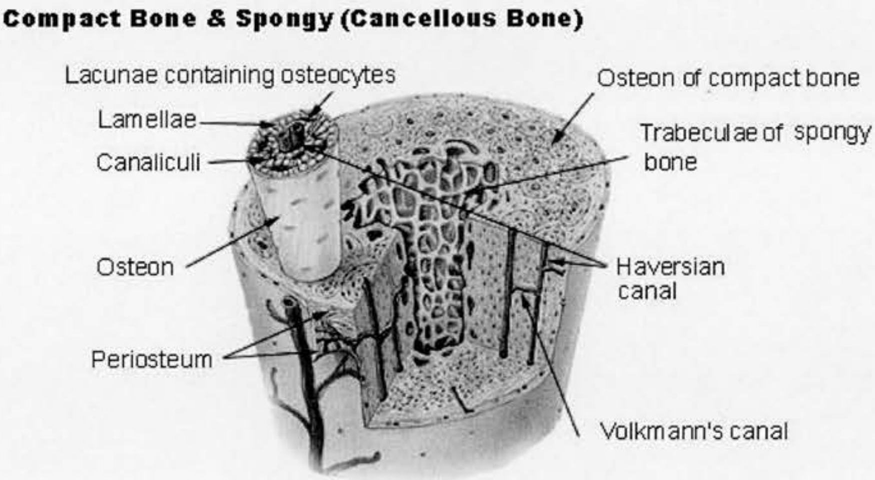
Figure 1. Anatomy of a long bone



Histologically bone contains cells surrounded by an extracellular matrix which is approximately 25% water, 25% collagen fibres and 50% crystallized mineral salts such as calcium phosphate, calcium hydroxide and calcium carbonate. Four types of cells are found in bone: osteogenic cells, osteoblasts, osteocytes and osteoclasts. Found in the inner portion of the periosteum, osteogenic cells are precursor stem cells derived from mesenchyme. They are capable of mitotic division and develop into osteoblasts. Osteoblasts synthesize and secrete collagen fibres and other components to produce the extracellular matrix and also initiate calcification. These osteoblasts then develop into osteocytes which maintain the bone metabolism. Lastly, osteoclasts are the cells responsible for resorption or breakdown of the extracellular matrix as a result of releasing certain lysosomal enzymes and acids. This normal homeostatic mechanism helps control calcium levels (26).

Distribution of these four types of cell plus the extracellular matrix varies as bone is not completely solid, but instead has many small spaces serving as channels for blood vessels and storage of marrow. Depending on the distribution, bone is labelled as either compact or spongy (Figure 2). Approximately 80% of the skeleton is compact bone which contains few spaces. It is found under the periosteum and, due to its strength, provides significant protection and support. It comprises many smaller units called osteons or haversian systems. Each contains a central canal which links to transverse perforating Volkmann's canals which carry the nerves, blood vessels and lymphatics from the periosteum. Each central canal is encompassed by rings of calcified extracellular matrix, known as lamellae, and between these are small lacunae containing osteocytes. Tiny canaliculi filled with extracellular fluid then connect the various lacunae with each other and the canals. Such haversian systems are not found in the remaining 20% of bone known as spongy or cancellous bone. It comprises lamellae arranged in columns called trabeculae which themselves contain lacunae and osteocytes. It is mainly found in the epiphyses and in a rim around the medullary cavity of long bones as well as in short, flat and irregular bones. In contrast to compact bone, spongy bone is light and provides storage and protection for red bone marrow (26).

Figure 2. Histology of compact and spongy bone



Bone formation during embryonic development is termed ossification and occurs in two ways: intramembranous or endochrondral ossification (26). In the former process (e.g. in flat bones of the skull), bone develops directly within mesenchyme arranged in sheet-like layers and in the latter it forms within hyaline cartilage that develops from mesenchyme. Endochondral ossification is the process by which the majority of bones form. Both mechanisms involve replacement of connective tissue with bone, but do not result in any differences in the structure of the mature bone. Different processes are also involved in bone growth during childhood. Appositinal growth, which results in increasing thickness of bone, is due to extracellular matrix deposition on cartilage surface. Growth in length is termed interstitial growth, and is due to further secretion of the cartilage extracellular matrix at the epiphyseal plate. Once bony growth is complete, there are still ongoing processes whereby old bone tissue is replaced by new in adults. Like many other physiological processes, this bone remodelling is under homeostatic control. This involves bone resorption in which osteoclasts remove minerals and collagen from bone, resulting in destruction of the extracellular matrix of bone, and bone deposition by osteoblasts in which the opposite process occurs. The rate at which remodelling occurs varies depending on the site and type of bone, and can also be influenced by factors such as exercise, diet and hormones. It is also involved in regulation of calcium homeostasis.

2.4.2 Mechanisms of Development of Bone Metastases

Metastasis is the process by which a tumour cell leaves the primary tumour, travels to a distant site and establishes a secondary tumour (27). Dissemination occurs either by direct spread, via haematogenous routes or the lymphatic system. However, tumours have variable metastatic potential and some have a predisposition for metastasis to specific sites (28). For example, breast, prostate and lung cancer frequently metastasize to bone. This can in part be predicted by the pattern of regional venous drainage, but blood flow patterns are not solely responsible for the pattern of spread. Other mechanisms felt to be involved in the selective attraction of certain tumour cells to specific organs include selective growth, adhesion and chemotaxis. Tumour cells extravasate equally around the body, but only grow in organs with the appropriate environment or growth factors, only adhere at specific sites and are attracted by specific factors released by the organ itself (24, 27).

The steps required for metastasis are similar for all tumour cells. It is not a random process, but involves a cascade of selective events involving interactions between tumour cells and the host microenvironment: invasion of tumour into adjacent normal tissues, penetration of blood and lymphatic vessels, release of tumour cells into the circulation, extravasation, adherence to endothelium with subsequent movement through the basement membrane, invasion, cell migration, and manipulation of the environment to promote tumour cell survival (24). In addition, angiogenesis, the generation of blood vessels, is essential to allow the primary site to grow and increases the chance of tumour cells reaching the circulation. This process is stimulated by angiogenic growth factors secreted by the tumour cells. Examples include transforming growth factor-α (TGF-α) and vascular endothelial growth factor (VEGF). Specific proteins are also responsible for other mechanisms in the process. Cell adhesion molecules (CAMs) are required for cellular attachment (e.g. integrins, laminin, E-cadherin), lysis of matrix proteins by proteinases (e.g. matrix metalloproteinases) and motility factors (e.g. fibronectin) are needed for invasion, and growth factors (e.g. Interleukin-8) are vital to stimulate cell proliferation at the distant site. All are potential targets for anti-neoplastic therapy.

Cells that metastasize to bone do so predominately via the haematogenous route. These tumour cells are capable of affecting the bone tissue via both osteoclasts and osteoblasts causing osteolytic bony destruction, sclerotic new bone formation or a combination of both types of metastases. The effects are in part due to tumour products altering the normal bone remodelling process. In fact a vicious cycle may ensue as the bone matrix itself contains multiple factors as a consequence of remodelling, which act as chemotactic agents for the tumour cells. Examples include type-1 collagen, osteocalcin, transforming growth factor-β (TGF-β), insulin-like growth factors I and II (IGF-I, IGF-II), and platelet-derived growth factor (PDGF). The increased osteoclastic activity which causes bone destruction is also a consequence of specific factors such as parathyroid hormone-related peptide (PTH-rP). This is in turn enhanced by TGF-β. Other mechanisms may be involved in osteoclast stimulation and mediators such as TGF-α, interleukin-1α (IL-1α), tumour necrosis factor (TNF), prostaglandin E, and IL-6 have been implicated. Osteoblasts also produce growth factors that can influence positively the growth of metastases. The newly formed bone may be laid down directly on trabecular bone surfaces with or without a preceding resorptive episode (27-29).

In summary, as a consequence of the above processes, the increase in bone turnover results in substantial skeletal deficits. An imbalance exists between the amount of bone resorbed and that formed at each remodelling site. In addition, due to a process known as uncoupling whereby episodes of resorption occur in succession, cavities are created that are never repaired subsequently. The converse happens when uncoupled bone formation causes osteosclerotic metastases (30).

2.4.3 Pain Pathways

The theory of pain has puzzled mankind since primitive times (31). Initially explanations varied from the influences of gods, magical fluids, frustration of desires and vital energy. In Ancient Greece philosophers such as Hippocrates, Plato and Aristotle considered the nature of pain. For example, it was felt to be either a consequence of excess or deficiencies of the four humours (blood, phlegm, yellow or black bile), or an emotion experienced in the heart. By Ancient Roman times, Galen had identified the concept of the central and peripheral nervous system, the role of the brain as the centre of sensibility, and "pain" nerves. In 1664 Rene Descartes described his theory in which nerves contained delicate threads spreading all over the body from their origins in the brain and served as organs of sense. In this Cartesian model, pain was viewed as a mechanical process of the body with a one-to-one relationship described between the amount or severity of the injury and the pain experienced. It also conceptualized the pain as being either physical or psychological. This work was a significant advance from previous theories as it described pain transmission from the periphery of the body to higher centres in the brain. However, it could not provide explanations for all pain phenomena and did not account for any modulation of the stimulus.

The next two major theories were the specificity theory and the intensive (summation) theory. The former postulated that pain was a specific sensation, like vision or hearing, independent of other sensations. In the latter theory, touch was only felt as a painful sensation once it reached a certain threshold. Again, there were gaps in the understanding. For example, they lacked the ability to explain pain in the absence of tissue damage or variation in pain between individuals.

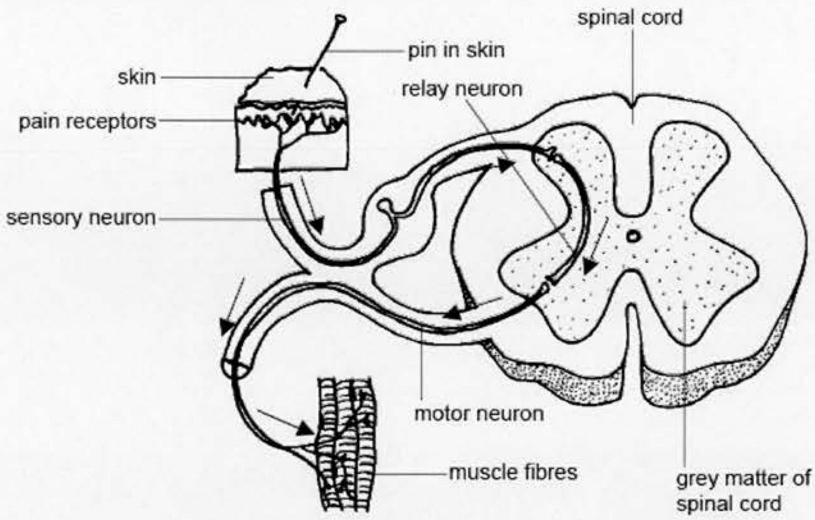
The largest development in understanding pain pathways was by Melzack and Wall in 1965: the Gate Control Theory (GCT) (32). This aided knowledge of the mechanisms of transmission and modulation of nociceptive signals and the recognition of pain as a psychophysiological phenomenon. The presumption was that "gates" in the dorsal horn of the spinal cord at each level determined which of the competing impulses was transmitted at any point in time. This transmission was affected by the stimulus intensity, other competing stimuli and by descending signals from the higher central nervous system (CNS). In essence, it illustrated continuous modulation of information rather than the one-way system described by Descartes. In the GCT, large and small fibres project into the substantia gelatinosa of the dorsal horn. The size of these fibres dictates transmission to the brain, with input from the large fibres inhibiting and input from small fibres facilitating transmission. There is also an element of central control in which input from the large fibres feeds back into the gate control system allowing the brain to identify, evaluate and modulate input before the action system is activated by the transmission cells. The action system comprises areas of the brain responsible for behavioural response to pain and the experience of pain itself. Since Melzack and Wall's original work, the theory has been modified. In 1968 and then 1983, Melzack and Casey updated the work to include excitatory and inhibitory links from the substantia gelatinosa to the transmission cells and descending inhibitory controls from the brainstem (33, 34). They also addressed the motivational, affective and cognitive aspects of pain. However, they were not able to explain several chronic pain syndromes.

Much more is now known about the neurophysiology and neuroanatomy of pain pathways and the current understanding is as follows (35, 36): when noxious stimuli are applied to the skin, a chain of events occurs that usually culminates in the perception of pain (Figure 3). At the start of this complicated process are nociceptors: the receptors for pain, discovered by Charles Scott Sherrington in 1906 (37). As a consequence of thermal, chemical or mechanical noxious stimuli, four main processes occur:

1) Transduction: the process of nociceptor activation, in which external noxious energy is converted to electrophysiological activity in primary afferent neurons. When this reaches a threshold value, an action potential is induced.

2) Transmission: involves the transfer of information via the dorsal horn of the spinal cord to the brainstem and thalamus. Connections are then established with higher brain centres involved with perception and affective responses to pain.
3) Modulation: regulation of the passage of nociceptive activity, especially at the level of the dorsal horn.
4) Perception: production of the various components of the pain experience.

Figure 3. Pain pathways



There are two types of primary afferent fibre involved in nociception: Aδ and C fibres. Each comprises a cell body in the dorsal root ganglion of a spinal nerve, and two axon branches which project to the periphery and CNS. Eighty percent of nociceptor primary afferents are C fibres. These are polymodal fibres which respond to mechanical, thermal and chemical stimuli. They are small, unmyelinated and conduct slowly (<3 metres/second), producing pain perceived a second or more after the stimulus is applied which subsequently increases in intensity over seconds or minutes and is felt as a chronic, burning, throbbing or aching sensation. In contrast, rapidly conducting (5-30 metres/second), larger diameter Aδ fibres are myelinated and respond to thermal and mechanical stimuli. The quality of this pain is generally felt to be sharp and prickling. Whilst fast pain is only felt in superficial tissues, slow pain may occur in the skin, and deeper tissues including visceral organs. A third type of primary afferent may also be involved in nociception under certain circumstances. Silent nociceptors (also known as mechanically insensitive afferents or MIAs) have very high thresholds, but in states of injury they may be activated (35, 36).

Ion channels that transform the noxious stimulus into action potentials are called transducers. At the outset, the mechanisms of transduction vary depending on the type of stimulus. Chemical stimulation with capsaicin, for example, and other vanilloid compounds, is known to activate the transient receptor potential, TRPV1 ion channel (previously called the vanilloid receptor, VR1). This triggers the influx of sodium and calcium and initiates nociceptive transmission. Another mechanism of activating nociceptive neurons is via acid-sensing ion channels (ASIC) which respond to reductions in extracellular pH. Transduction of painful thermal stimuli also occurs via specific ion channels. As well as being activated by capsaicin, TRPV1 is activated by heat. TRPV2 (previously known as the vanilloid receptor-like protein, VRL-1) may also contribute to heat pain at higher temperatures. Several ion channels are gated by decreases in temperature resulting in pain with cold stimulus: TRPM8 and TRPA1. However, overlap is seen as certain chemical agents may also activate these ion channels: the cooling agent menthol has also been shown to activate TRPM8 and mustard oil may activate TRPA1. Less is known about the mechanisms involved in transduction of painful mechanical stimuli in comparison to chemical and thermal stimuli. Activity of these transducers induces membrane depolarization and generates action potentials via influx of sodium and calcium ions through gated channels, and this subsequent increase in intracellular calcium concentration activates intracellular second messenger pathways (35, 36).

After stimulus transduction, transmission of nociceptive information along the neuronal axon ultimately leads to release of transmitters at central synapses. In the transfer of nociceptive signals to higher centres, a large variety of amino acids and neuropeptides act as neurotransmitters in the dorsal horn. Inhibitory amino acids include γ-aminobutyric acid (GABA) and glycine, whilst glutamate and aspartate acting on N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-

isaxazole propionic acid (AMPA) receptors are the main excitatory amino acids. Excitatory peptide neurotransmitters include substance P (SP), calcitonin gene-related peptide (CGRP) and bradykinin. In contrast, galanin, somatostatin, neuropeptide Y (NPY), neurotensin, and opioids such as enkephalins and β–endorphins are inhibitory. The distribution of these neurotransmitters in tissues varies (35, 36).

Primary afferent neurons enter the spinal cord via the dorsal roots prior to terminating by synapsing with CNS neurons in the dorsal horn. The dorsal horn itself is anatomically divided into ten sections known as Rexed's laminae (I-X). Normal tactile input from Aβ fibres enters in laminae III, IV and V, whereas nociceptive fibres synapse in the more superficial areas; lamina I, the marginal zone and lamina II, the substantia gelatinosa. However some Aδ fibres also terminate in lamina V, as do most visceral afferents. The nociceptive afferents form links with either excitatory, inhibitory or projection neurons to regulate the nociceptive input to the brain. Three types of projection neurons are involved in such transfer of information (35, 36):

1) Nociceptive-specific cells (NS): these are mainly found in lamina I, but are also seen in laminae II and V. They respond only to noxious stimuli and have small receptive fields.
2) Low-threshold (LT) neurons: found in laminae II and IV and respond only to innocuous stimuli.
3) Wide dynamic range (WDR) neurons: predominately found in lamina V, but also in lamina I, and respond to a wide range of sensory stimuli.

Ascending pathways are responsible for transmitting nociceptive signals from the spinal cord to the brain. Several pathways exist: spinothalamic, spinoreticular and spinomesencephalic. The spinothalamic pathway is traditionally the main pain pathway; it comprises both NS and WDR neurons, and is subdivided into the lateral neospinothalamic tract and the medial paleospinothalamic tract. Both project to the thalamus, but the former carries aspects of pain such as location and intensity, whereas the latter is thought to mediate emotional perceptions of pain. Whilst the spinothalamic tract neurons start in laminae I, V-VII, the spinoreticular pathway originates from laminae VII and VIII. They terminate in the reticular formation of the medulla and pons, prior to relaying to the thalamus. Nociceptive neurons in the spinomesencephalic tract originate in laminae I and V and end in the midbrain. This pathway is felt to be implicated in the modulation of pain signals. From the nuclei of the thalamus, nociceptive signals are projected to multiple cortical areas, resulting in a pain experience comprising sensory and affective components (35, 36).

Perception of pain may vary and hence it is clear that there is more to the pain pathway than simply the transmission of signals from the noxious stimulus to the brain. Such modulation of signals potentially may occur at any point along the pathway, but most is known about modulation in the dorsal horn of the spinal cord. Such modulation involves the endogenous opioid system, segmental inhibition, activity of nociceptive and other afferent inputs, and descending control. The main action of endogenous opioids in laminae I and II is via presynaptic inhibition of injury-evoked neurotransmitter release from primary afferents, but postsynaptic inhibition is also seen. Segmental inhibition is primarily mediated by endogenously released GABA acting on pre and postsynaptic mechanisms and by postsynaptic inhibition by glycine. Other substances involved in segmental inhibition include cannabinoids, nitric oxide, cholecystokinin (CCK) and galanin. The descending control of nociceptive signals is via two pathways. In the midbrain, one pathway originates in the peraqueductal gray matter and descends via the nucleus raphe magnus in the medulla to inhibit dorsal horn neurons in laminae I, II and V. Similarly, a second pathway descends from the locus ceruleus in the midbrain to the medulla and spinal cord. Two neurotransmitters predominate in this descending control: serotonin (5-HT) and norepinephrine (noradrenaline) (35, 36).

Whilst basic descriptions of pain pathways (mainly cutaneous nociception) have been elucidated above, these explain the physiological processes in response to acute noxious stimuli. However, a number of important mechanisms occur in response to persistent pain. With ongoing pain, increased responsiveness of primary afferent neurons and spinal cord neurons results in two closely related phenomena:

hyperalgesia and *allodynia*. Hyperalgesia is an increased response to a normally painful stimulus due to increased excitability of primary afferent neurons. Allodynia occurs when pain is felt after a normally innocuous stimulus. This excitability of primary afferents is known as *peripheral sensitisation*. Sensitisation involves changes in neurons that alter their response to stimulation. When noxious stimuli sensitise nociceptors, they induce physiological, neurochemical and morphological changes in the primary afferent neurons. This dynamic *plasticity* ultimately results in the development and maintenance of hyperalgesia. Various extracellular mechanisms may be responsible in the pathway to increased sensitisation of primary afferents: voltage-gated ion channels, transducers, ligand-gated ion channels, G-protein-coupled receptors and tyrosine kinase receptors. For example, usually innocuous stimuli are subsequently able to cause action potentials in nociceptors (via voltage-gated sodium and potassium channels) and this may also occur spontaneously. The normally silent receptors which do not respond to natural stimuli, in response to tissue injury and inflammation, may become active. In addition, action potentials may result from a stimulus of fixed intensity, but at increased frequency. Upregulation of ion channels and increased production of both receptors and neurotransmitters are other changes which contribute to increased nociceptor excitability. Another route to increased excitation of primary afferents is via prolonged activation of receptors by inflammatory mediators, such as neurotrophin nerve growth factor (NGF), bradykinin, serotonin, prostaglandin E2 and cytokines. The result is post-translational (e.g. phosphorylation) and transcriptional changes in the composition of nociceptors (35, 36).

Hyperexcitability of the primary afferent neurons may subsequently trigger and maintain excitability of spinal cord neurons in the dorsal horn resulting in *central sensitisation*. Similarly to the periphery, as a consequence of post-translational and transcriptional changes, spinal cord neurons are more likely to generate action potentials. However, the central mechanisms are complex due to the cellular and synaptic network of the dorsal horn. Three physiological changes are apparent in the dorsal horn neurons: reduction in activation threshold, increased responsiveness, and expansion of the receptive field (the area in which stimulation leads to a response of a particular afferent neuron). In addition, a number of particular phenomena are seen. The first of these is *wind up*. This occurs when C fibres and Aδ are repeatedly stimulated at frequency of 0.3-10 Hz and summation of the excitatory postsynaptic currents causes pain that persists for seconds after the stimulus has stopped (38). *Long-tem potentiation* (LTP) may be evoked by input of several bursts of short duration, high frequency stimulation which leads to an augmented pain response lasting minutes after the stimulus has ceased. This type of stimulation may also lead to a third pattern called *long-term depression* (LTD) in a different sub-group of spinal neurons. In this case, there is a prolonged reduced responsiveness. However, this too may contribute to enhanced excitability via disinhibition. As well as increased excitatory input from primary afferent neurons (in particular as a consequence of glutamate, tachykinin, brain-derived neurotrophic factor and NMDA and AMPA receptor activity), two other mechanisms contribute to the development of central sensitisation. There is reduced inhibitory input to spinal cord projecting neurons (via inhibitory neurotransmitters such as GABA, catecholamines and serotonin) and synaptic reorganisation in the dorsal horn. Lastly, spinal cord glial cells (astrocytes and microglia), as well as providing a supportive environment, have been implicated in development of central sensitisation. Activation of these cells may also lead to cytokine release and increased sensitivity of spinal cord neurons. Both peripheral and central processes contribute to hyperalgesia in the immediate area of injury (primary hyperalgesia), but when hyperalgesia is found in an adjacent area, such secondary hyperalgesia is due only to central sensitisation (35, 36).

2.4.4 Pathophysiology of CIBP

The mechanisms responsible for the generation and maintenance of CIBP are not clearly understood. However, knowledge of the pathophysiology is slowly increasing. To understand why malignant bony disease is painful involves investigation at each of the steps in the pain pathway: primary afferents, factors within the bone and changes within the spinal cord. This is summarised in an excellent review by Urch and the main points are described below (39):

- The periosteum, bone marrow and mineralized bone are richly innervated by primary afferents. Aδ fibres express NPY and vasoactive intestinal peptide

(VIP) and C fibres express CGRP, TRPV1 and sympathetic neurons (SNS). VIP and CGRP as well as SP and glutamate have been implicated in bone metabolism.

- Tumour growth results in induction of a pronounced inflammatory infiltrate. Tumour cells release a variety of growth factors (e.g. nerve growth factor), cytokines (TNF), chemokines, interleukins (IL-1, IL-6), prostanoids, endothelins which activate primary afferents.
- Tumour growth activates primary afferent fibres resulting in an alteration of the osteoblast/osteoclast balance. RANK is the receptor activator for nuclear factor κB expressed on osteoclast precursors and the ligand (RANKL) is expressed on several cell types including osteoblasts. The RANK-RANKL interaction is needed for normal balanced activation of osteoclasts secondary to osteoblasts. To maintain balance, RANKL is inhibited by a cytokine secreted by osteoblasts, called osteoprotegerin (OPG), which reduces osteoclast differentiation and activation (40). However, cancer cells may secrete RANKL and sequester OPG, disrupting the balance.
- Cancers generate an acid environment which can activate directly nociceptors such as ASIC and TRPV1.
- Significant alterations also occur in the dorsal horn of the spinal cord in CIBP (see below).

It is via these mechanisms that CIBP is understood to occur, rather than the prior belief that pain was simply due to vascular occlusion or compression of the bone or peripheral nerves due to mechanical instability.

To gain understanding of many of the pathophysiological mechanisms of pain in general, animal studies were vital. The same was true for understanding the mechanisms of pain secondary to bony malignancy as described above (39). However, prior to 1999 there was no accepted animal model of cancer pain secondary to bony disease. This was remedied by Schwei at al who injected osteolytic sarcoma cells into the intramedullary space of the mouse femur (41). The aim of this work was to characterise the extent of cancer-induced bone destruction, the sensory innervation of the bone, the animal behaviour indicative of pain and the neurochemical changes occurring in the spinal cord and primary afferent neurones. To evaluate the development of a nociceptive state, the mice were observed at 21 days post injection during handling and after normally non-noxious stimulation. The mice were then killed and their spinal cords and dorsal root ganglia immunohistochemically analysed and the femora were processed and assessed radiologically for evaluation of bone destruction (osteolysis). Compared with controls, animals injected with sarcoma cells demonstrated significant bone destruction with subsequent guarding when being handled, and a positive nociceptive behavioural response which correlated significantly with the extent of bony destruction. The development of sarcoma did not induce any obvious changes in the innervation of mineralised bone or the periosteum. However, three significant alterations were seen in the spinal cord neurochemistry after tumour injection that were not seen in any of the other experimental groups. The first of these was expression of dynorphin in a subpopulation of dorsal horn neurons in the deep laminae of the spinal cord. This correlated significantly with the extent of bony destruction. (Dynorphins are a class of opioid peptides which exert their effect via the κ-opioid receptor and modulate pain response.) Secondly, a significant increase in the number of spinal cord neurons expressing c-Fos protein was found. This also correlated positively and significantly with the extent of bony destruction. In addition, normally non-noxious mechanical stimulation of the femur induced a significant increase in the number of c-Fos expressing lamina I neurons in animals with bony disease. (C-Fos is a proto-oncogene and one of a small group of primary response genes. Its protein product, Fos, is an integral component of complex signalling mechanisms believed to be responsible for cells response to stimulation. It is used as a marker for monitoring neuronal activities in the central pathways of the sensory system.) Normally non-noxious stimulation also induced substance P receptor (SPR) internalisation in a significant number of lamina I neurons in sarcoma-injected animals. The third, most striking, change was a massive astrogliosis in the ipsilateral spinal cord segments receiving primary afferent input from the femur. Astrocyte hypertrophy without neuronal loss was demonstrated and correlated with bony destruction. This may be important as astrocytes express glutamate-aspartate transporters which help regulate the extracellular levels of excitatory amino acids. The hypertrophied astrocytes also release cytokines and growth factors which alter the neurochemical environment (41).

An advantage of the model developed by Schwei et al., was that it approximated human disease well both in terms of localised pathological findings and painful behaviour. The mouse model study indirectly showed (via SPR internalisation and c-Fos expression) that after extensive tumour-induced bone destruction, primary afferent neurons are sensitised. This sensitisation and the neurochemical changes also correlated with the extent of disease and destruction. The authors concluded that the bone cancer induced a profound reorganisation of the spinal cord that may reflect the central sensitisation seen in other chronic pain states (41).

The changes demonstrated in the study above suggested that the pathophysiology of CIBP is unique from solely inflammatory or neuropathic pain. This is understandable as clinically many analgesics have varying efficacy depending on the underlying cause of the chronic pain state. The pathophysiological distinctiveness of CIBP has been explored in other publications. In a paper by Honore et al., as well as the astrocyte, dynorphin and c-Fos changes, specific markers were examined in bone, inflammatory and neuropathic pain models (42). To create the CIBP model, sarcoma cells were again injected into the intramedullary canal of the mouse femur. To create the inflammatory model, mice received an injection of complete Freund's adjuvant (CFA) into the hindpaw. For neuropathic pain, sciatic nerve transection or L5 spinal nerve ligation (SNL) were performed. Behavioural, radiological and immunohistochemical analysis was carried out as well as an assessment of the effects of morphine. All three models demonstrated measureable pain-associated behaviours such as mechanical allodynia. In the inflammatory pain model, increases were seen in SP, CGRP, protein kinase C and SPR in the spinal cord. In the neuropathic pain model, levels of SP and CGRP fell, and increases in galanin and NPY were seen in the spinal cord and primary afferent neurons. In either site, none of these markers altered in the CIBP model. The authors concluded that the murine model of CIBP shares key features with human CIBP and that inflammation, nerve injury and cancer each generate unique changes in the spinal cord and dorsal root ganglion (42).

Since these initial models in mice, other models have been developed using tumour types in other animals. Medhurst et al. described the first known model of CIBP in the rat (43). Intra-tibial injections of mammary gland carcinoma cells resulted in extensive damage to the cortical bone and trabeculae with subsequent reduction in activity and development of mechanical allodynia (hind paw withdrawal response to von Frey filament stimulation), hyperalgesia (paw pressure) and reduced weight bearing. Significant enhancement of glial fibrillary acidic protein (GFAP) staining in the spinal cord was indicative of glial cell activation and involvement of astrocytes. Urch, Donovan-Rodriguez and Dickenson also used a rat model of CIBP to examine the dorsal horn neuronal responses in detail (44, 45). In 2003, they used electrophysiology to characterise natural (mechanical, thermal and cold) and electrical-evoked responses of superficial and deep dorsal horn neurons after intra-tibial injection of mammary tumours in rats (44). As in previous studies, behavioural tests showed progressive development of evoked mechanical allodynia and hyperalgesia. Repetitive noxious stimulation of primary afferent fibres was shown to produce the wind up phenomenon. Significant increases in C fibre responses were seen in both superficial and deep neurons in the CIBP model compared with the sham animals. Neurons were classified as NS or WDR based on their responses to mechanical and thermal stimuli. A difference in the ratio of these neurons was seen in the lamina I area in CIBP animals: the proportion of WDR neurons increased (almost doubled). In addition, there was an increase in the A fibre evoked response in the superficial WDR neurons. More neurons were relaying innocuous as well as noxious stimuli directly to central pain centres. There was also a significant increase in the peripheral receptive field in superficial neurons. NS neurons remained unaltered. The authors speculated that these lamina I changes may cause increased excitability in lamina V neurons and may increase activation of affective and autonomic responses to painful stimuli. The results demonstrated the hyperexcitability of dorsal horn neurons (central sensitisation) in CIBP. They also showed that the behavioural hyperalgesia and allodynia correlated and emerged in parallel with the dorsal horn neuronal changes (45).

Animal models have also been useful when looking at the role cancer-induced osteolysis plays in bone pain (46). It has been shown that tumours increase the number and size of osteoclasts at sites of tumour and that they are required for cancer-induced bone destruction (47). Honore et al. treated mice with CIBP with OPG to block osteolysis before it occurred by disruption of the RANK-RANKL interaction (48). The result was reduced bone destruction and less pain. Improved behavioural measures of pain and allodynia were seen, although pain was not relieved completely. No significant reduction in tumour burden was observed, but there was a dramatic decrease in osteoclast numbers. However, changes were also seen in the spinal cord with administration of OPG. Dynorphin and GFAP levels were reduced to basal levels. C-Fos levels also decreased, but not to basal level. The same was true of SPR internalisation. This work demonstrated that excessive tumour-induced bone destruction is involved in the generation of CIBP. It also provides evidence of a possible target for new therapies. Another possible novel target is the TRPV1 receptor as selective blockade has also been shown to attenuate bone pain (49).

Another issue to consider in the pathophysiology of CIBP is that, although there is a general correlation between extent of bone remodelling and pain, there are many situations in which patients have significant bony disease without pain and vice versa. Such heterogeneity has been explored by Sabino et al. (50). In this study, the intramedullary cavity of mice femora were injected with sarcoma, melanoma or colon adenocarcinoma tumour cell lines. The results showed that the extent, pattern and type of bone modelling differed depending on the type of cell line injected. Only sarcoma-bearing animals induced a significant increase in numbers of activated osteoclasts. Pain-related behaviours also differed. Sarcoma-bearing mice showed significant spontaneous guarding behaviour as a measure of ongoing pain, but this was not seen in the other models in comparison to sham animals. For ambulatory pain, sarcoma and colon-injected mice displayed extensive guarding, but this was minimal in the melanoma group. Lastly, allodynia was assessed and found to be present in both sarcoma and melanoma, but not colon cancer CIBP models. Thus, Sabino et al. suggest that the unique pain state in each cancer type reflects activation of a variety of nociceptors that innervate the bone (50). Different tumours release varying proteins, cytokines and factors which can activate primary afferent nerve fibres. Distinctions were also seen in markers of peripheral and central sensitisation such as c-Fos expression, dynorphin expression, SPR internalisation and levels of GFAP. All these markers were increased in sarcoma-bearing mice, but increases were only seen in some of the markers with melanoma and colon bone cancers. The authors conclude that multiple factors are involved in the generation and maintenance of CIBP.

In a review article, Halvorson et al. also looked at the differences between primary cancer types using sarcoma and prostate tumours to compare primarily osteolytic with osteoblastic disease respectively (51). Sarcoma-bearing animals showed significant bone destruction, but little evidence of bone formation. In contrast, prostate-bearing models induced significant new woven bone with increase in number of osteoblasts, as well as evidence of concurrent bone destruction. Both models were characterised by osteoclast proliferation and hypertrophy. Both sets of animals demonstrated pain-related behaviours, but these were more pronounced in the sarcoma mice, perhaps due to increased mechanical stability of the bone in the prostate cancer mice (51). Changes were seen in the sensory innervation of bone with sarcoma tumour cells seen to destroy the distal processes of sensory fibres, whereas simultaneous injury and sprouting was seen with the prostate-bearing animals. The authors suggest that a component of CIBP is due to tumour-induced injury of the primary afferent fibres.

As well as assessing neurochemical changes that occur in the spinal cord and dorsal root ganglia in animal models of CIBP, work has been undertaken to address the response to various pharmacological agents in these models. In their research, both Honore et al. (42) and Medhurst et al. (43) showed that large doses of morphine reduced pain-related behaviour significantly. Urch et al. demonstrated that chronic systemic morphine attenuated pain behaviour to a greater extent than acute systemic morphine (52). In addition, reduction in pain correlated with reduction in the hyperexcitability of superficial dorsal horn cells, although the abnormal ratio of WDR:NS neurons persisted. Luger et al. injected sarcoma cells into mouse femur and compared this with mice with inflammatory pain (CFA) (53, 54). As with other CIBP models, significant bone destruction and bone cancer pain-related behaviours were seen. Sarcoma animals showed lower von Frey thresholds (a measure of movement evoked pain), longer guard times, greater incidences of flinching (a measure of background pain), lower incidences of limb use, greater disability on rotarod (a measure of ambulatory pain), and increased guarding and flinching on response to palpation. The authors showed that the pain generated was alleviated with systemic opioids, producing a dose-dependent suppression of pain behaviour. Interestingly, the doses of morphine required in the bone pain model were ten times more than in the mice with inflammatory pain. This was not felt in full to be due to the intensity of the various pain syndromes, but due to differences in underlying mechanisms, underlining the theory that CIBP is a unique pain state, but with some changes indicative of both inflammatory and neuropathic origin. Other studies have assessed the impact of opioids in animal models of CIBP (55-57) and a variety of other pharmacological treatments have been tested such as acetaminophen (56, 57), non-steroidal anti-inflammatory drugs (56, 57), cyclo-oxygenase (COX)-2 inhibitors (43, 56-58), tricyclic antidepressants (56), selective serotonin reuptake inhibitors (56) and anticonvulants (56, 59). In particular, gabapentin was found to normalise the dorsal horn pathophysiology, reducing significantly the electrical and mechanically-evoked responses of WDR neurons, in addition to normalising the ratio of WDR to NS neurons (59). After cessation of treatment with gabapentin, the dorsal horn reverted to the hyperexcitable state. Donovan-Rodriguez et al. suggest that the effects of gabapentin may result from potential actions on altered voltage-dependent calcium channel activities, reducing transmitter release and the activation of the spinal superficial neurons that drive the plasticity (59). The same team also demonstrated that ondanstetron, a selective 5-HT_3 antagonist, reduced significantly mechanical and thermal-evoked responses in a CIBP rat model, suggesting a role for descending serotonergic facilitation in CIBP (60). The various drugs used in these animal models will be discussed further in Chapter 3.

In summary, these murine models are felt to be representative of human CIBP. The tumour cell lines result in increased osteoclastic activity and bone destruction, followed by the development of both background and incident pain and associated pain behaviours, all of which continues to escalate with the possibility of fracture. This pattern arises from activation and destruction of primary afferents stimulated by various mediators secreted by cancer cells and the invading immune infiltrate, increased activation of osteoclasts via RANK-RANKL interaction and acidosis, and unique changes and plasticity within the dorsal horn (39). Understanding this sequence of events and the underlying pathophysiology in animal models allows advancement of the management of CIBP in patients.

2.5 Clinical Features of CIBP

Bony metastases cause considerable morbidity. Despite the fact that two thirds of demonstrated sites of bony disease are painless, CIBP is frequent and is the most common cause of cancer-related pain (8). It has not been found to correlate with type of tumour, location, number and size of metastases, gender or age (61). Unfortunately, it is often one of the most difficult symptoms to treat, in part due to the fact that the pain may be a mixed syndrome with a variety of symptoms, and may be disproportionate to the extent of bone disease. It differs from other types of pain, and comprises clinically of three components (39). The first of these is ongoing or *background* pain. The other two components are types of *breakthrough pain*: *spontaneous pain* and *incident* (movement-related) *pain*.

Background pain is typically a constant dull ache, although in the initial stage it may be intermittent in nature. It may be localised to a specific site of bony disease or may be generalised due to multiple metastases. In some cases it may result in referred pain. The pain also tends to increase progressively with the evolution of the disease (54). Breakthrough pain is defined by Portenoy as "a transitory exacerbation of pain that occurs on a background of otherwise stable pain" (62). When breakthrough pain is spontaneous it occurs unexpectedly without trigger. Conversely, incident pain occurs as a result of either a voluntary (e.g. walking) or involuntary (e.g. sneezing) act. Individuals may have both predictable and unpredictable breakthrough pain as part of their clinical scenario. Typically, breakthrough pain is moderate or severe, frequent, of rapid onset and is of short duration (62, 63). Usually this pain is more difficult to palliate as the doses of opioid required to control it may cause significant unwanted side effects. Characterisation of CIBP has allowed examination of this in more detail. The Palliative Care Research Team in Edinburgh showed that breakthrough CIBP pain (pain on movement or spontaneous pain at rest) was more severe in intensity than background pain at rest (64, 65). Half of these patients with movement or spontaneous pain reported that the duration was less than 30 minutes, and 25% reported a duration of less than 15 minutes. Half of patients also felt that this pain was unpredictable. With the onset of analgesia from immediate release morphine usually taking 30 minutes, the pain may resolve prior to medication taking effect. In this situation, adverse opioid effects are more likely to predominate. In addition, the practice of anticipatory analgesia, which involves use of analgesic treatment prior to movement, is impossible in many circumstances. The presence of breakthrough pain is felt to be a marker of a generally more severe pain syndrome, and is associated with both pain-related functional impairment and psychological distress (63).

Janjan et al. examined the presenting symptoms of 108 patients referred to a multi-disciplinary clinic for bone metastases (6). Median time from diagnosis to the development of significant symptoms associated with bony metastases was 22 months, ranging from two weeks to 23 years. Pain was a presenting symptom in 74%. At its worst, pain was rated as severe by 78%. On average, pain was rated as moderate to severe in 79% and severe in 23% of patients. However, only 45% reported "good relief" from their prescribed analgesics. Clearly bone pain has a significant impact on patient well-being and is often undertreated. This issue and the management of bone pain are discussed in the subsequent chapters.

2.6 *Complications of Bone Metastases*

Complications of bone metastases result in increased morbidity and reduced quality of life. In addition to CIBP, complications include pathological fracture, spinal cord and nerve root compression, marrow suppression and hypercalcaemia. The frequency of these skeletal events varies depending on the tumour type and treatment, but on average, a patient with metastatic bone disease will experience an event every three to six months (25).

Hypercalcaemia is a metabolic complication of bony disease and may be associated with significant morbidity if unrecognised. It occurs in approximately 10-40% of cancer patients during their illness, although extent of bony disease does not correlate with hypercalacemia (8). However, in most instances, hypercalaemia is secondary to bone destruction and thus osteolytic metastases are present in 80% of cases (22). Factors produced by the tumour itself stimulate osteoclastic bone resorption and increased renal tubular calcium reabsorption is also found (28). A serum calcium level of >3mmol/L may result in symptoms such as fatigue, constipation, gastrointestinal upset and confusion. Higher levels are considered a medical emergency with renal impairment, deteriorating conscious level and cardiac arrhythmias. Management initially comprises hydration and bisphosphonate medication followed by treatment of the underlying cause. Certain malignancies, for example breast, renal, lung (squamous) and myeloma, are more prone to the development of hypercalcaemia than others (21, 22, 25).

Pathological fracture is a consequence of bone metastases in 8-30% of patients, although is most commonly seen in patients with breast cancer and myeloma. This is in part due to the lytic nature of the lesions in these patients and the subsequent bone fragility (8). Likelihood of fracture increases with the duration of the disease and as such is more common in patients with better prognosis, bone only disease as they survive longer than those with extraosseous disease. The most frequent sites of pathological fracture are the vertebrae, ribs and proximal long bones (21, 22, 25). Treatment of the pathological fracture is usually surgical although it is partially dependent on the site, and thus specific techniques vary. If surgical intervention is required, the main goal is to remove as much tumour as possible and is followed by the use of bone cement and fixation. Lower limb fractures are usually treated in this way, but fractures of the arm may be treated conservatively. Lesions in the spine may also be treated conservatively, but in a minority the best option is surgical decompression and stabilisation. In most centres, the standard care post-operatively is radiotherapy to inhibit local regrowth and to induce recalcification (21, 25). Certain features have proven useful in assessing the risk of impending fracture. These include pain exacerbated by movement, site of the lesion, radiological characteristics and tumour size (66). If fracture is likely, then orthopaedic referral for consideration of prophylactic fixation should be sought. Typically this is also followed with radiotherapy. Such treatment should help to restore function and reduce pain (24), but the potential benefits must be weighed up against the surgical risks and likely patient survival.

One potentially serious consequence of vertebral collapse is spinal cord compression which can occur in approximately 5% of patients (24). Both cord compression and nerve compression may result due to mechanical injury, when a metastatic lesion lies near to neurological structures. Typically this causes localised pain, neuropathic pain and progressive neurological symptoms. Pressure on the vascular supply also contributes to the injury as a consequence of ischaemia, venous stasis and infarction (8). Spinal cord compression is an oncological emergency and early detection and treatment are necessary for retaining neurological function. It has been shown that the most important predictor of survival in this situation is the ability to walk after treatment (67). However, signs and symptoms may develop slowly, making early diagnosis a challenge. One study examining presenting symptoms of patients with bone metastases, found that 10% of patients had previously undiagnosed spinal cord compression, although a significant proportion of the patients in the study had spinal involvement (6). Weakness, sphincter disturbance and sensory loss are later signs (22). Depending on each individual case, treatment may comprise corticosteroids, radiotherapy and/or surgical decompression.

Pancytopenia may result from bone marrow infiltration due to generalised bony involvement. Patients are then at higher risk of complications such as bleeding and infection, and as such, treatment with chemotherapeutic agents becomes increasingly problematic.

2.7 Consequences of Bone Metastases and CIBP

Because of the potential for a prognosis measured in years, patients are now living longer with the consequences of bone metastases. As a result of the issues already discussed, such as pain, fractures, neurological deficits and hypercalcaemia, patients may experience associated anxiety and depression and poor quality of life (24, 68). Depression, social and physical functioning have all been shown to predict poor quality of life in patients with bony metastases (5). The incidence of mood disturbance in cancer pain increases with higher levels of disability, advanced illness and pain (8). In addition, there are social implications such as impact on relationships and the ability to work, with subsequent financial costs (6). As such, patients with CIBP are a particularly vulnerable group. There are also the wider issues to consider such as increasing demands on health care resources and health economics.

Chapter 3 MANAGEMENT OF CIBP

Treatment of bone metastases is primarily palliative. The main aim of treatment is to restore mobility and function, and to relieve CIBP for the remainder of the patient's lifespan. In addition, prevention of potential complications of bony disease, such as pathological fractures, is important. To enable an appropriate individually tailored management plan to be agreed for patients with CIBP, a thorough assessment is vital. The issues relating to assessment of CIBP are discussed in Chapter 4.

3.1 Principles of Treatment of CIBP

The priorities for treatment of CIBP are patient-dependent. They need to take into account both patients' and clinicians' ideas, concerns and expectations as well as practical issues, such as type and stage of cancer, co-morbidities and prior treatment. In addition, although the treatment of CIBP should be evidence-based, practices will vary among physicians and place of care. Local resources may be a major consideration. Overall however, treatment of CIBP will usually involve a combination of different modalities and strategies, such as symptomatic treatment of background and breakthrough pain and treatment of the underlying cancer. This was demonstrated in a prospective observational cohort study looking at treatment modalities employed in patients with CIBP (69). Thirty-two patients were followed up for a mean of 22 weeks, during which time 19 different treatment modalities were used, representing 6.75 interventions per patient or an equivalent of 1.2 interventions every four weeks. Various papers have summarised the management of bone metastases and CIBP (8, 24, 25, 64, 70-72). An overview of the various available options is discussed below.

3.2 Analgesics for Background CIBP

The basic principles of treatment of pain are similar regardless of whether the pain is due to bony metastases or another aetiology. Underpinning this are guidelines from the World Health Organization (WHO) in which a three-step analgesic ladder for cancer pain relief is used to suggest treatment depending on the pain severity and nature (73) (Figure 4). As pain intensity increases, strength of the analgesic required increases up the ladder from non-opioid (step 1) to weak opioid (step 2) to strong opioid (step 3). At steps two and three, non-opioids may also be used in combination with opioid treatment. In addition, underlying physiology may suggest the need for adjuvant analgesics which can be added into every treatment step.

Figure 4. World Health Organization 3-step Analgesic Ladder

STRONG OPIOID (e.g. morphine)
+/- Non-opioid
+/- Adjuvant

Pain persisting or increasing

WEAK OPIOID (e.g. codeine)
+/- Non-opioid
+/- Adjuvant

Pain persisting or increasing

NON-OPIOID (e.g. paracetamol)
+/- Adjuvant

Initial treatment depends on any existing medication regimen and should start at the step of the ladder appropriate to the severity of pain. If there is no prior treatment as per the WHO guidelines, then treatment should begin at step 1. Analgesia should be titrated against the patient's pain report to the optimal level. If at any stage pain is no longer relieved, then treatment should move to the next step. In conjunction with this, certain general principles should be considered. The dosing schedule will depend on the drug's pharmacokinetics, but regular administration ('by the clock') for continuous pain is desirable. The preferred route of administration is oral, but alternative routes should be considered depending on specific circumstances, such as bowel obstruction. At all points on the ladder, consideration should be made for factors such drug tolerability, toxicity, interactions and contra-indications to ensure treatment is on an individual basis. Using the WHO ladder for treatment, cancer pain should be controlled in approximately 70-80% of patients (74, 75).

As well as the WHO analgesic ladder, other guidelines exist to aid cancer pain management, such as the Scottish Intercollegiate Guidelines Network (SIGN) (76) and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (77). Both detail the current evidence for treatment of cancer pain in general as well as specific guidance for management of CIBP.

3.2.1 Non-Opioid Analgesics

Paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) are now universally accepted for the treatment of cancer pain (76). However, recommendations are mainly based on studies in non-malignant pain which are extrapolated to treatment of pain in cancer, due to lack of specific randomised controlled trials (RCTs) in this area. Paracetamol is a relatively safe drug with minimal side effects at recommended dosages. There is evidence that its analgesic effect is central and due to activation of descending serotonergic pathways, but the main site of action is likely to be inhibition of prostaglandin synthesis (78). NSAIDs have been shown to be more effective than placebo alone in cancer pain, but there is no clear verification to support efficacy of one NSAID compared with another (79), and potentially serious toxicities such as gastrointestinal bleeding and renal dysfunction are well recognised. Thus, patients with mild pain should be given either drug based on the risk:benefit ratio for each individual. As described above, they can also be added at higher steps of the ladder to stronger analgesics for moderate and severe pain (80). There is no evidence to support the use of both paracetamol and an NSAID together, although this too is felt to be acceptable.

One area of growing interest is that regarding selective cyclo-oxygenase (COX)-2 inhibitors. In addition to their role for treatment of cancer pain, there is a suggestion that they have beneficial anti-tumoural and anti-angiogenic properties both in animal models (58) and human cancer cell line studies (81). However use of these drugs has fluctuated due to concerns over cardiovascular risk.

In CIBP, research into the use of non-opioids has been conducted in a mouse model, although the results are conflicting. One study showed that oral administration of paracetamol and indomethacin (a non-selective NSAID) produced an analgesic effect (57), whereas in another study neither of these drugs improved pain behaviour (56). Similarly to trials in patients using varying methodology and assessment tools, these disparities may be a consequence of lack of standardisation. In patients with CIBP, evidence for use of non-opioids is lacking. NSAIDs are felt to be useful in metastatic bone pain due to reduced production of prostaglandins via inhibition of the COX pathway of arachidonic acid breakdown. In addition, direct action on spinal nociceptive processing has been demonstrated (8). However, although a meta-analysis did show analgesic efficacy in patients with cancer pain, it did not find conclusive evidence in CIBP, due to a lack of comparable studies (82).

3.2.2 Opioid Analgesics

For treatment of cancer pain, the second step of the analgesic ladder involves the use of weak opioids such as codeine or dihydrocodeine. These may be combined with paracetamol (e.g. cocodamol 30/500) and NSAIDs which have the potential to reduce the dose of opioid required and possible opioid side effects. On the third step of the ladder, morphine is the strong opioid of choice (83) due to its documented efficacy and safety (74, 75). Although morphine is the most commonly used strong opioid, there are now numerous alternatives (oxycodone, diamorphine, alfentanil, buprenorphine, fentanyl, hydromorphone and methodone). Multiple formulations provide flexibility of treatment, but in view of variation in drug metabolism both between and within individuals, choice depends on the balance of efficacy and side effects. As with non-opioid drugs the oral route is preferable as it is simple and acceptable (83). However, the use of alternative routes such as transdermal, subcutaneous (SC) and intravenous (IV) is well recognised. For example, preparations such as fentanyl patches may be suitable for someone with vomiting or problems swallowing, but the pain needs to be stable in view of their long duration of action. The schedule of administration depends on the opioid preparation. For example, immediate release drugs usually require four hourly administration, whereas most modified release medications need twelve hourly dosing. It is generally accepted practice to start patients on an immediate release preparation with short duration of action, to allow rapid control of their pain and appropriate titration of dose. Thereafter this can be changed to a longer acting, modified release preparation once the pain has stabilised. It is important at all stages of titration to prescribe extra doses for breakthrough pain (see below). If at any point the balance between toxicity and efficacy is unfavourable, then it is appropriate to consider switching to an alternative opioid. There is a lack of evidence as to choice of opioid, and so it should be tailored to the patient, again depending on factors such as side effect profile, route of administration, response to treatment and renal function. For guidance on appropriate conversion rates for switching opioids, an expert opinion should be sought (76). It is also important to be diligent in preventing nausea, vomiting and constipation whilst on opioids, and as such prophylactic anti-emetics and laxatives should be considered. Additionally, other factors such as a renal dysfunction and signs of opioid toxicity require monitoring.

As with non-opioid analgesics, studies have been conducted to assess the impact of opioids on CIBP in mouse models. Tramadol, fentanyl and morphine have all been shown to be effective in this setting (52, 56, 57). In addition to antinociceptive properties, one study also showed reduction in cancer cell-induced bone lesions, although there are many unanswered questions regarding the mechanism by which this occurs (55). However, research by Luger et al. (as described in Chapter 2) has shown that treatment with opioids in the mouse model indicates that CIBP may have a unique pathophysiology. The doses of morphine required to inhibit nociceptive behaviours was tenfold greater than in inflammatory pain (53). In patients with CIBP, opioid medication also provides the foundation of analgesic treatment. However, the clinical basis for efficacy in bone pain is less strong than in animal models.

3.2.3 Co-Analgesics / Adjuvants

Hanks in 1985 described a co-analgesic as "any drug (or device) which may not have intrinsic analgesic activity, but which when used with a conventional analgesic will contribute significantly to pain relief" (71). Since then the number of possible co-analgesics or adjuvants available has increased, but the principles are the same; their effective use is dependent on first identifying the underlying pain mechanism involved. For example, for pain of a neuropathic origin, the use of antidepressants and anticonvulsants is well recognised. A number of Cochrane reviews are available on the use these drugs for pain (84-86). Saarto and Wiffen reviewed 61 RCTs to determine the analgesic efficacy and safety of antidepressants in neuropathic pain (84). Tricyclic antidepressants (TCAs) were found to be effective, as was venlafaxine. However, side effects from drugs such as amitriptyline may limit their tolerability. There was limited evidence for the use of selective serotonin reuptake inhibitors (SSRIs). Wiffen et al. looked at RCTs of anticonvulsants for acute and chronic pain (85). Out of 26 trials considered eligible, only one study considered cancer pain. Overall, although there was no evidence for use of carbamazepine and gabapentin in acute pain, the authors concluded that two-thirds of patients with chronic pain would be expected to achieve good pain relief. Similar findings were found in a separate systematic review specifically addressing gabapentin (86). Pregabalin has also been shown to be effective in relieving neuropathic pain (87). It is also an anticonvulsant, which like gabapentin, is now licensed for this indication. Capsaicin is also licensed for neuropathic pain, but its use may be limited by an intense burning sensation during initial use. Ketamine, an NMDA antagonist, and lidocaine (lignocaine) IV may also be of benefit, but are for specialist use only (88).

As with studies in analgesics, much of the evidence for use of the drugs described above is in the non-malignant setting. However, as the underlying pathophysiology responsible for neuropathic pain is felt to be similar in both malignant and non-malignant neuropathic pain, their use in cancer pain is accepted (76). Looking specifically at CIBP there is even less evidence relating to use of adjuvants despite their frequent use. However, animal models of CIBP have looked at the action of anticonvulsants and antidepressants. In a mouse model, El Mouedden and Meert found that TCAs reduced pain behaviour significantly, but only at sedative doses and gabapentin had no effect (56). In contrast, Donovan-Rodriguez et al. found that in a rat model of bone pain, gabapentin normalised the CIBP-induced dorsal horn neuronal changes and attenuated pain behaviour, suggesting that this may be a useful clinical treatment (59). This research is being advanced in a multicentre, double-blind Randomised Controlled Trial (RCT) of pregabalin versus placebo in conjunction with XRT for CIBP in patients (89).

Corticosteroids are well established co-analgesics (8). As well as benefits such as improvement of appetite and fatigue, and reduction of oedema associated with spinal cord compression, they have been shown to improve the pain of bony metastases (90, 91). However, again RCTs are lacking and the side effects of longer term steroid use need to be considered. Another additional option for treatment of CIBP is a 5% lidocaine (lignocaine) patch. There is no evidence for its use in cancer pain, but anecdotally it is of benefit for specific sites of malignant bony pain. Calcitonin, by reducing osteoclastic bone resorption, has been examined for use in CIBP. In a Cochrane review there was no evidence that calcitonin was effective in CIBP, that it reduced analgesic consumption or controlled complications due to bone metastases (92). In addition, its use is limited by its short duration of action and rapid development of tachyphylaxis. Nitrous oxide, used to supplement conventional analgesics, has also been investigated for CIBP (93). It has been shown to be safe and effective as a 50:50 mixture with oxygen for episodic pain from bony metastases, but this was a very small study so further research is warranted.

3.3 Analgesics for Breakthrough CIBP

In addition to a basal analgesic regimen, all patients with CIBP should be prescribed "rescue" analgesia for breakthrough pain (BTP). The general principles for treatment of background cancer pain also apply to BTP and should be based on the WHO guidance using non-opioid, weak and strong opioids and adjuvants (73). However, because BTP is usually rapid in onset, moderate to severe in intensity and of short duration (62, 63), certain issues need additional consideration.

In view of the nature of BTP, immediate release opioid preparations are favoured for patients with moderate to severe pain. This means that as much as possible the pharmacokinetics of the drugs try to mirror the timing of the BTP. However, titrating opioids for BTP can be difficult, not because of the lack of response to opioids, but rather the doses required to control the BTP produce unacceptable side effects when the patient is resting (8, 72). Therefore, use of NSAIDs may be useful for incident pain if problematic toxicity from opioids occurs once the BTP disappears (94). Conventionally, for patients on regular morphine, the BTP dose is calculated as a proportion of the around-the-clock (ATC) dose. The ratio of 1:6 has been adopted so that the BTP dose is equivalent to a four hourly dose of morphine or a sixth of the ATC dose. Thereafter, as the doses of regular ATC morphine are adjusted, the BTP dose should also be maintained at the same ratio (76). However, there are no RCTs as confirmatory evidence of this method (83).

The RCTs looking at BTP in cancer pain have focused on the use of oral transmucosal fentanyl citrate (OTFC) (95). With a rapid onset of analgesia in 5-15 minutes and short duration of action of two hours, it is felt to be an effective treatment for BTP in cancer patients (83). However, in contrast to the way of calculating BTP analgesia as a proportion of the ATC dose, no relationship was found between total daily dose of fixed opioid regimen and dose of OTFC required to manage BTP (96). Therefore, using this method for BTP, the dose should be titrated individually. Other routes of administration, such as intranasal and sublingual, are also being investigated to look for more rapid onset of action, but as yet these products are not licensed for this use. In some situations parenteral rescue medication may be necessary to enable prompt relief of BTP.

For patients with CIBP, it is important to consider both spontaneous and incident BTP, as different management approaches are required. If incident BTP is predictable (for example, due to walking) then advice is generally to take analgesia in anticipation of a precipitating episode (97). When taken at an appropriate time in advance this allows the analgesic action to take effect prior to activity. Unfortunately, not all pain is predictable. This was demonstrated in a study to characterise CIBP in patients attending the Edinburgh Cancer Centre for palliative XRT (65). Seventy-two subjects were asked to complete the Brief Pain Inventory (BPI), McGill Pain Questionnaire (MPQ) and a Breakthrough Pain Questionnaire

(BTPQ). The study found that 52 patients (72%) had episodic pain, but 27/52 (52%) of patients with this BTP were unable to predict when their pain was going to flare up. In addition, 36/52 (69%) of patients with BTP (50% of whole sample) reported that the duration of pain was less than 30 minutes, and it was less than 15 minutes in 30/52 patients (58%). Hence, using short acting opioids prior to movement, as routinely advised, may be inadequate in a group of individuals with intense, unpredictable and brief episodes of pain. As a consequence, side effects may predominate. It has also been noted that the underlying neurobiology of movement and spontaneous pain may result in poor opioid-responsiveness to these components of BTP (64).

To explore the options for optimising opioid therapy for CIBP, Mercadante et al. implemented an experimental paradigm to assess whether incident pain was preventable by reducing the hyperexcitability of spinal cord neurons (98). In this study, 25 patients with movement-related CIBP received rapid intravenous titration of opioid dose to obtain pain relief at rest. This was then increased until the maximum dose was achieved as determined by limiting side effects, despite having achieved control of background pain. Doses were then stabilised or reduced according to individual requirements. The results showed that control of background pain was achieved using this paradigm. In addition, this produced an acceptable level of incident pain intensity. The authors conclude, therefore, that it is important to optimise background pain to improve movement-related CIBP. Another option tried as a method of maximising opioid treatment of CIBP is the use of psychostimulant drugs, such as methylphenidate. This has been shown to allow patients to tolerate higher doses of opioids by reducing sedation in between episodes of BTP (99).

In summary, although traditional drugs from the WHO ladder are used in cancer BTP, few prospective studies provide confirmatory evidence. It is vital, therefore, to follow certain principles: to explore the underlying mechanism of the pain to decide the most suitable analgesic, along with ensuring that the treatment matches the temporal characteristics of the BTP.

3.4 Bisphosphonates

Bisphosphonates are now a standard management for prevention and treatment of complications secondary to bone metastases. The trial evidence has been summarised in a series of reviews (100-102). However, it should not be forgotten that as well as reducing skeletal-related events (SREs) such as fractures and hypercalcaemia, bisphosphonates have a role in treatment of pain.

Current SIGN guidelines for control of cancer pain suggest that "bisphosphonates should be considered as part of the therapeutic regimen for the treatment of pain in patients with metastatic bone disease" (76). Various formulations are available including oral clodronate, IV pamidronate, and newer, more potent third generation compounds such as IV zolendronic acid and ibandronate (which can be given either orally or IV). They do not replace conventional analgesic therapy, but should be used as adjuvant treatment. The evidence for their usage comes from two large systematic reviews (103, 104). Carr et al. examined 30 trials including 4464 patients (103). Conclusions were difficult due to the heterogeneity of the bisphosphonate trials. This was as a result of a number of factors including different inclusion criteria, use of concomitant medications and XRT, disease categories, dosage regimens, choice of agent, duration of follow up, and varying methods of pain assessment and outcome measures. However, the majority of studies showed a positive effect, in agreement with data published by Wong and Wiffen in 2002 (104). In this review, 30 RCTs were included with a total of 3682 patients. The number needed to treat (NNT) to gain analgesic benefit was eleven at four weeks and seven at twelve weeks. However, due to small numbers in the sub-groups, it was not possible to compare the effectiveness of different bisphosphonates or the response according to the underlying primary tumour type. Only one study in the review looked at the effect of bisphosphonates on quality of life and found a small improvement in the treatment group at four weeks.

More recent articles have examined the role of bisphosphonates further. In reviews in 2006 (105) and 2007 (106), the authors summarised that oral clodronate, IV pamidronate and IV zolendronic acid have all shown an analgesic effect in CIBP. Ibandronate (oral and IV) was shown to be effective for CIBP in breast cancer patients for up to two years. However, both papers concluded that there is still a lack of comparative studies to evaluate superiority of one formulation over another for CIBP. Body also looked at safety considerations (105). Although generally well tolerated, occasionally side effects are seen. The major toxicities of concern with bisphosphonate use are renal dysfunction and osteonecrosis of the jaw. In addition, oral drugs may cause gastrointestinal upset, IV administration may cause flu-like symptoms and all formulations have the potential to result in hypocalcaemia. Therefore vigilance in monitoring renal function, calcium levels and oral examination (and education) is necessary to prevent additional morbidity and discontinuation of treatment. Supplemental calcium and vitamin D may be advised if dietary intake is poor. Newer uses of bisphosphonates being investigated include treatment of CIBP with high-dose bisphosphonates, treatment of cancer-treatment induced bone loss and preventative therapy in primary cancer management (105).

Bisphosphonates act by preventing bone loss by binding to and accumulating at active sites of bone remodelling. There is a direct effect on osteoclast-mediated bone resorption with inhibition of osteoclast maturation and function leading to osteoclast apoptosis. Induction of apoptosis occurs by two modes of action: non-nitrogen containing bisphosphonates, such as clodronate, cause apoptosis via formation of cytotoxic metabolites, whereas the nitrogen-containing compounds, such as ibandronate, inhibit protein tyrosine phosphatases (107). They also inhibit protein prenylation and so interfere with intracellular processes, such as organisation of the cytoskeleton (108). Initially, bisphosphonates were developed for use with osteolytic metastases, but it is now recognised that they also have effects in osteoblastic disease. Studies suggest that there is direct anti-tumoural activity via blockade of angiogenic pathways, immunomodulatory effects, inhibition of osteoclastogenesis and by inhibition of tumour cell adhesion and invasion of the extracellular bone matrix (108). However, the exact mechanisms by which bisphosphonates relieve pain are unknown. It is felt that multiple mechanisms may be responsible, including reduced acidosis, growth factor release and peripheral sensitisation of neurons (109).

Halvorson et al. studied the use of IV ibandronate in a mouse model of CIBP (107). They demonstrated rapidly attenuated ongoing and movement-related pain-related behaviour with the bisphosphonate treatment. The sarcoma mice showed increased osteoclast proliferation and an increase in macrophage infiltration when compared with sham animals. Although ibandronate reduced the extent of bone resorption and induced extensive tumour cell necrosis, it did not reduce significantly the osteoclast proliferation. However, it did prevent significantly the expression of c-Fos neurons and upregulation of dynorphin in the spinal cord. Thus, the authors conclude that ibandronate treatment, not only attenuates tumour-induced activation and injury of sensory fibres in the bone, but also reduces the neurochemical changes in the peripheral and central nervous system. Also, by reducing the acidic microenvironment created by osteoclast and tumour cells, ibandronate decreases the activation of ASICs expressed by sensory neurons that innervate tumour-bearing bone.

3.5 Radiotherapy (XRT)

XRT is the gold standard treatment of CIBP. Therefore, all patients with pain from bone metastases which is difficult to control by pharmacological means should be referred to a clinical oncologist for consideration of external beam XRT (76). However, pain is not the only indication for XRT for bony disease. Only about a fifth of treatments are specifically for CIBP (110). Other reasons for treatment include prophylactic and post-operative management of pathological fracture, and neurological complications such as spinal cord compression or nerve root involvement (111).

Numerous studies have been conducted to address issues such as the optimal dose and fractionation schedule, as many regimens exist. A number of excellent systematic reviews have summarised the evidence. McQuay et al. published a Cochrane review in which 20 RCTs reported on 43 different XRT fractionation schedules and eight studies of radioisotopes (discussed below) (112). XRT produced complete pain relief at one month in 25% of patients, and at least 50% relief in 41%

of patients at some time during the trials. There were no differences in pain outcomes between single and multiple fractions of XRT, and similarly no differences were seen for adverse effects. However, figures for speed of onset of relief or duration of relief could not be obtained from the pooled results. In the largest trial, 52% of patients who had complete relief achieved this within four weeks, and median duration of complete relief was 12 weeks (7). The authors conclude that, given equivalent efficacy between schedules, clinical choice should be a balance between adverse effects, impact of the schedules on quality of life, prognosis and cost (112).

In 2003 Sze et al. also published a systematic review of RCTs of single fraction versus multifraction XRT (113). Twelve studies were included in the meta-analysis. In agreement with the review by McQuay, the data revealed no difference between single and multiple fractions for relief in CIBP. Overall pain response rates were 60% in the single fraction group and 59% with multiple treatments. Equivalent complete response rates were 34% and 32% respectively. However, differences were seen between the schedules for complications of bony disease. The single fraction arm had higher re-treatments rates (21.5% vs 7.4%) and higher pathological fracture rates (3% vs 1.6%), although spinal cord compression rates were similar. A number of additional issues were raised in the review; minimal data was available to examine quality of life and health economics, and the lack of a standard criterion created problems in assessing pain control. Definitions of response also varied between studies. In an attempt to promote consistency between future studies, an international consensus statement has been published (114, 115). Assessment of CIBP is discussed further in Chapter 4.

In 2007 Chow et al. repeated the work described above with the aim of updating previous meta-analyses (116). In 16 RCTs they confirmed again that overall there was no difference between schedules for treatment of CIBP. However, there was some evidence that certain groups may benefit from a protracted schedule, such as those with CIBP with a neuropathic component. Single treatments may suit frailer patients or situations where cost or convenience is an issue. In the review, a trend towards increased risk of pathological fracture and spinal cord compression with single treatment was seen, but this was not significant statistically. However, the authors did confirm the concerns regarding higher re-treatment rates with single fractions. Whether this is of concern is debatable, as despite the fact that overall 25% of patients require re-treatment, this is felt to be feasible, safe and effective (117). Response after re-treatment is similar to that with the primary treatment. The best timing of further XRT is not clear, but waiting at least four weeks is advised.

Generally, localised external beam XRT is well tolerated, with minimal side effects (117). Toxicity is related to the total dose and fraction size. With treatment of larger areas, patients may experience nausea and anorexia, and prophylactic anti-emetics may be given. Another issue is a phenomenon known as pain flare. This is a temporary worsening of pain shortly after XRT for CIBP. Incidence varies depending on the exact definition used in trials. Chow et al. found that 14% of patients receiving external beam XRT had pain flare on day one after treatment, with overall incidence ranging from 2-16% over the study period (118). Loblaw et al. found a higher incidence of 34% that lasted a median of three days (119). They also found that single fraction XRT may have a greater risk of flare than multiple fraction schedules. Presence of pain flare may predict future response to treatment.

Much of the work described above relates to use of external beam XRT for localised bony disease. If patients have multiple, widespread sites of CIBP then either wide-field (hemi-body) XRT may be an option or alternatively radiopharmaceutical treatment (see below). In wide-field XRT, large external beams are used to cover painful areas either above or below the umbilicus (117). It is an effective treatment and responses may be rapid, but this has to be weighed up against increased toxicity, such as gastrointestinal upset and bone marrow suppression. In addition, tolerance of specific organs (e.g. lung) needs consideration. Hospitalisation may be recommended for symptomatic relief after treatment.

In view of the fact that systematic reviews of the literature have called for more attention to be placed on quality of life outcomes after XRT for CIBP, Wu et al.

explored the effect of treatment on functional interference as measured by the Brief Pain Inventory questionnaire (120). They found a significant reduction for all seven functional interference items after XRT. General activity showed the greatest improvement. In a patient-centred approach to looking at quality of life for those undergoing XRT for CIBP, Szumacher et al. looked at patients' treatment preferences (121). In this study 76% of patients felt they would want to play an active or collaborative role in the decision making process, rather than a passive role. In patients who stated this preference, 76% favoured a single fraction and 24% wanted 2000 cGy in five fractions. Older retired patients were more likely to opt for the single treatment. Both the convenience of the treatment plan and the risk of pathological fracture were important factors in the decision making process.

The pathophysiological mechanisms by which XRT exerts its effect on CIBP are not understood fully, but current understanding is discussed later in the thesis (along with potential prognostic factors and predictors of response to XRT).

3.6 Radioisotopes

Radioisotopes are considered for treatment of CIBP when conventional analgesics are unable to control multifocal sites of pain. Systemic treatment leads to concentration of radioactive substance at sites of tumour with delivery of a localised radiation dose (usually by emission of short-range beta particle irradiation). Hoskin in 1995 summarised the early options for radiopharmaceutical treatment (111). Radioiodine (^{131}I) was shown to be selectively taken up by bone metastases from thyroid cancer, although pain relief was less effective than with XRT. Early studies also examined the use of radioactive phosphorus (^{32}P), but marrow suppression limited its use. Current options for use include strontium-89 (^{89}Sr), samarium-153 (^{153}Sm) and rhenium-186 (^{186}Re). These specific bone seeking isotopes are taken up preferentially at sites of osteoblastic activity associated with bone metastases. ^{89}Sr and ^{153}Sm are the most commonly used. Both are given intravenously on an outpatient basis. As with external beam XRT, a number of systematic reviews have assessed their clinical utility.

McQuay et al. reviewed eight RCTs of radioisotopes for CIBP (112). They reported a similar extent of relief, onset and duration as XRT. Two of the included studies showed significantly fewer new pain sites with strontium versus XRT alone (122, 123). Quality of life was also better with radioisotope use in a study combining radioisotope with XRT versus XRT with placebo (122). However, more haematological toxicity was seen with radioisotope use.

The evidence for strontium use was examined by Bauman et al. in 2005 (124). They reviewed six phase III RCTs, two phase II RCTs and one randomised crossover trial of ^{89}Sr. The methodology and controls varied, but overall they recommended its use. The same was true of ^{153}Sm after reviewing three phase III and two phase II RCTs. In addition to this, 17 trials (phases I-III) studied rhenium, but its use was still felt to be experimental. In this review, where histology was specified, 80-90% of patients had prostate cancer, 5-10% had breast cancer and a similar proportion had lung cancer reflecting the fact that most research into radiopharmaceuticals has focused on prostate cancer. In tumours, such as renal cancer, where osteoblastic disease is uncommon a poor response would be expected (125). However, trials looking at a wider variety of histological types are lacking.

Radioisotopes were also reviewed by Finlay et al. in 2005 (126). They summarised that treatment with radioisotopes was effective for reduction of CIBP with response rates of between 40% and 95%. Pain relief typically began between one and four weeks after administration and continued for up to 18 months. As a consequence of treatment, many patients were able to reduce their analgesic requirements. Pain relief was also seen with repeated doses. Response to ^{89}Sr was found to be most effective in patients with limited skeletal involvement, better performance status and osteoblastic lesions. In comparison to XRT, the data generally implied similar response rates with ^{89}Sr. Toxicity was mainly haematological, but the thrombocytopenia and neutropenia was usually mild and reversible. Pain flare was seen in 15% of patients treated with ^{89}Sr and 12-20% using ^{153}Sm. Finlay et al. confirmed that the effectiveness of radioisotopes may be increased when combined with other agents such as cisplatin. Also of interest is the fact that some studies of

^{89}Sr and ^{153}Sm showed a reduction in the number of hot spots on bone scans and falling tumour marker concentrations suggesting a possible tumouricidal action.

In summary, radioisotopes all appear to be effective for CIBP with fairly equivalent toxicity profiles. Therefore the decision on which to use may depend on other factors such as local policy, cost and personal preference.

3.7 Chemotherapy

Pain relief is not typically the main reason for administering chemotherapy, but treatment of the underlying cancer may aid pain management. The exact value of this is not known (127). This stems from the fact that although it is clear that systemic chemotherapy is effective for treatment of bony metastases, quality of life data, in particular data on pain relief, are lacking. However, because the analgesic effect depends on the chemosensitivity of the underlying tumour, response is likely to be better in metastases due to lymphoma, myeloma and testicular cancer than renal cancer (72). A balance between potential benefit and toxicity needs to be considered carefully on an individual basis, especially in frail patients with advanced disease.

3.8 Hormonal Therapy

The same principles apply to treatment with hormone therapy as chemotherapy. The evidence for use of drugs such as tamoxifen, aromatase inhibitors, anti-androgens and gonadotrophin-releasing hormone analogues in hormone sensitive breast and prostate cancer is well established. Again, studies have focused on time to progression and overall survival rather than analgesic benefit. In this group of patients, disease progression may be slow and patients may live for years with bone-only disease. Therefore, hormonal therapy may be an appropriate option for treatment of the underlying cancer and possible pain management.

3.9 *Orthopaedic / Surgical Intervention*

In view of the fact the pathological fractures are a complication of bony metastases in 8-30% of patients, it is not surprising that surgical intervention is frequently required. It is important that pathological fractures are stabilised to alleviate pain and facilitate mobility and recovery. The type of surgery required will depend on the kind of fracture and clinical situation. Surgical stabilisation may improve dramatically the quality of life, reduce the pain and prevent complications associated with immobility (8). In cases of impending fracture, prophylactic pinning may also improve CIBP and recovery from elective surgery is likely to be faster than after a more aggressive procedure.

Spinal instability is a cause of back pain in about 10% of patients with metastatic bone disease (25). It may cause movement-related incident pain, which can be difficult to treat. Approximately 85% of metastases causing spinal instability arise anteriorly from the vertebral body and stabilisation is essential for pain relief (8). Various surgical techniques are available. One option is vertebroplasty (cementoplasty) which involves percutaneous injection of polymethylmethacrylate bone cement into the bone cavity. This technique has been advanced with the use of balloon kyphoplasty which uses an inflatable balloon to restore vertebral height prior to introducing the cement. Complications are said to be rare, but include problems such as intravascular leakage and local irritation, compression and ischaemia (128). Studies have confirmed that these techniques can provide sustained pain relief for patients with CIBP, with improved function and quality of life (129, 130). Cement can also be used to palliate other sites of CIBP (e.g. pelvis). SIGN guidelines now recommend the use of such procedures with appropriate patient selection (76).

In some cases, surgical intervention may not be in the patient's best interests, for example if co-morbidities render a general anaesthetic too risky or life expectancy is short. In these situations conservative management may be used to aid pain relief. Protection with orthotic devices such as a light-weight functional brace may increase comfort, and use of prostheses or mobility aids may improve quality of life in patients with CIBP. Multi-disciplinary team involvement with communication between surgeons, oncologists, palliative care physicians, physiotherapists, occupational therapists and specialist nursing staff is vital.

3.10 Radiological Intervention

Radiofrequency ablation is a new method of controlling CIBP. In this technique, tumour is destroyed by local application of a high frequency alternating current guided by imaging. This has been shown to be a safe and well tolerated technique with significant reduction in pain and analgesic requirements (131). Alternative methods include chemical ablation (ethanol or acetic acid) and thermal therapies (laser, microwave, ultrasound and cryoablation) (132).

3.11 Anaesthetic Techniques

In the small proportion of patients with bone pain which is unresolved despite using the principles already described, anaesthetic intervention may prove beneficial (76). Patients most likely to benefit are those with significant locally advanced disease, neuropathic pain or problematic movement-related pain. Regional nerve blocks achieve analgesia by blocking a primary nociceptive afferent or by disrupting the nerves transmitting to higher centres (8). As a consequence they are most efficacious for localised pain. Spinal administration of local anaesthetics with an opioid may provide analgesia in suitable cases. More invasive techniques such as percutaneous cordotomy and neurodestructive processes are reserved for patients with intractable pain, as serious complications are a major risk (133).

3.12 Future Treatment Options for CIBP

In an era of targeted treatments, new agents are being explored for the treatment of CIBP, thanks to experimental studies in animal models providing insight into underlying mechanisms. Possibilities for treatment are summarised by Lipton et al. (134) and Coleman et al. (135) and include:

- OPG: a cytokine which inhibits differentiation and maturation of osteoclasts via disruption of the interaction between RANK and RANKL.
- Selective endothelin-A receptor antagonists (Atrasentan/ABT-627): block the proliferative effects of endothelin-1 in prostate cancer
- Denosumab (AMG-162): human monoclonal antibody which targets RANKL
- Vitaxin: human monoclonal antibody to integrin $\alpha v\beta 3$ with anti-angiogenic properties
- Cathepsin K inhibitors
- Src inhibitors
- Chloride channel inhibitors
- PTHrP antibodies
- TGF-βR1 kinase inhibitors

3.13 Supportive Care

The approach to a patient with CIBP should be holistic, aiming to treat other symptoms or problems in addition to CIBP. In conjunction with the various different treatment modalities described above, consideration should be given to complementary therapies, such as massage, acupuncture and transcutaneous electrical nerve stimulation (TENS). A case study detailing the successful use of TENS for treatment of CIBP has recently been published (136). Addressing psychosocial and spiritual issues, which may impact on the pain experience, may be beneficial. Work addressing evidence-based standards for cancer pain management also advocates patient education about pain management (137).

3.14 Evaluation of Response to Treatment

One of the most important issues to consider in the management of patients with CIBP is that follow-up is vital to allow optimal management of pain which may not remain stable (137). It is likely that over a period of time, the nature of the pain will change in some way due to changing pathophysiology (138). Reassessment should be undertaken in a time-scale appropriate for each individual, meaning that efficacy and tolerability of a treatment can be judged, and adjusted as necessary. Various criteria are used to evaluate the response of bone metastases and CIBP to treatment (24). This partly reflects the aims of treatment: to relieve pain, to prevent pathological fractures, to improve mobility and function, and to prolong survival. Thus, the assessment should involve a combination of clinical history and examination, pain evaluation, assessment of function and quality of life, use of radiological imaging, and tumour markers where appropriate. The various tools and issues regarding assessment of CIBP are discussed in Chapter 4.

In summary, management of CIBP should be multi-factorial with symptomatic drug treatment used in an integrated way with disease-modifying therapy and non-pharmaceutical measures (83). Above all, this must be tailored to the individual taking into account the clinical circumstances and quality of life issues. However, despite current knowledge of the multiple approaches which can be utilised to manage CIBP, treatment remains a challenge (139). The reasons why this may be are also discussed in Chapter 4.

Chapter 4 PAIN ASSESSMENT

The importance of a comprehensive evaluation of the management of cancer pain has been established (140). However, pain is a personal experience and thus difficult to define and to measure. Pain assessment is a vital preliminary step towards the satisfactory control of cancer pain (73). There are no direct objective measures of pain and so measurement relies on the patient's report. As a consequence it is difficult to get an accurate estimate of cancer pain prevalence. Studies are reported in varying settings and patient groups and the assessment tools used may differ. Any measure of pain must be graded appropriately to identify any changes, must be clear to both patients and clinicians, user-friendly and must be shown to be valid and reliable. Thus the situation is complex. This chapter addresses the issue of pain assessment, in particular focusing on assessment of CIBP.

When assessing pain a number of aspects are essential:

1) Clinical history
2) Physical examination
3) Diagnostic investigation
4) Pain evaluation

4.1 Clinical History

All patients should have a detailed history taken as part of their initial assessment, but also on subsequent consultations. Typically, we are taught that this first assessment should include the history of the presenting complaint, past medical and psychiatric history, medication history including allergies, systemic enquiry, family and social history (141). It is useful to gain some understanding of the patient's home and personal circumstances as this may impact on management options. Being aware of a history of drug or alcohol abuse is valuable, as is knowing whether there is a background of cognitive problems. Establishing rapport with the patient may also provide important information. Future history taking will not require repeat questioning on all of these points, but it is important to adapt to each individual's situation at each assessment at different points in time.

In addition to the detail above, it is essential in an oncological assessment to know the patient's cancer stage, including the primary site, histology and extent of disease, as well as their previous and current anti-neoplastic therapy. The careful history taking should also include a thorough pain history. It is sometimes of value to encourage the patient to describe their pain in detail without interruption. Thereafter further information can be sought on specific characteristics of the pain including:

- Onset
- Main site
- Radiation
- Character / quality
- Severity
- Duration
- Frequency and periodicity (temporal pattern)
- Special times of occurrence
- Aggravating factors
- Relieving factors
- Response to analgesics
- Response to other interventions
- Associated phenomena (physical and psychological)
- Interference with activities of daily living (ADLs)

Patients with CIBP will often experience a combination of background and breakthrough pain and therefore the characteristics of both types of pain should be sought. Furthermore, a history of prior pain syndromes and their treatment should be requested, as this is likely to have a bearing on subsequent management. This may be useful, not only in learning what therapeutic options may be beneficial, but also it may provide insight into a patient's ability to cope and their degree of social support during difficult times. Psychosocial assessment is particularly important during the cancer journey, as it may have a direct influence on a patient's pain experience. Although it is difficult to prove interdependent relationships, mood disturbance is associated with cancer pain (142). When all these aspects are addressed together it should provide an indication of the patient's "total pain". This is a concept, introduced by Saunders in the 1960s, which describes pain as combining physical, emotional, social and spiritual elements (143). All of this information may then allow speculation as to the causality of the pain and should guide appropriate examination and investigation.

4.2 Physical Examination

As with history taking, physical examination should be a routine but vital part of the patient assessment for those with or without pain. However, it must be undertaken with care as it has the potential to exacerbate pain. The possible benefits should outweigh the costs. Traditionally, physical assessment comprises general observations followed by examination of the various systems: cardiovascular, respiratory, gastrointestinal, genitourinary, nervous and locomotor. For example, observation of a patient's demeanour, complexion, nutritional status and movement may provide a wealth of information prior to any physical contact. In cancer patients with pain, it may not be necessary to assess every system, especially in frailer patients who may not tolerate extensive examination. However, examination should nonetheless be thorough and focus on the painful and any other relevant areas. Neurological examination is often particularly important in the setting of CIBP.

4.3 Diagnostic Evaluation

A major part of the assessment of CIBP is the diagnosis and monitoring of bony disease. A number of radiological methods of assessment are available. They should be used to complement clinical evaluation of the patient, but not be the focal point of assessment.

4.3.1 Plain Film Radiography

The simplest and most patient friendly investigation is plain film radiography. It is commonly used to evaluate symptomatic sites and confirm findings on other imaging studies. It is useful to assess the risk of pathological fracture (144). Appearance on plain film may allow characterisation of a lesion and can help distinguish metastases from other conditions. Helpful features include cortical destruction, appearance of periostitis, orientation of the axis of the lesion and the zone of transition. This last characteristic represents the border between the lesion and normal bone. If wide, it is likely to be an aggressive process and if narrow is usually benign. It is the most reliable indicator on plain film (145). However, plain film is not without its disadvantages. A change of about 40% in bone density is required to detect bone metastases and as such smaller lesions remain undetected (8). It does not allow visualisation of the whole skeleton and also it is generally not recommended as a screening tool due to relatively poor sensitivity.

4.3.2 Bone Scan (Scintigraphy)

The radioisotope bone scan is widely used and has been the standard initial imaging method of bone metastases for many years. It allows assessment of the extent of bony involvement. Tracer accumulates in areas of reactive new bone formation which form in response to disease. The amount of accumulation is sensitive to the level of blood flow. As a result, most metastatic lesions are "hot", but in lesions with little reactive bone or poor blood flow, they may be "cold". Widespread disease results in diffuse accumulation and gives the appearance of a "superscan" (144). An advantage of bone scans is that they are more sensitive than plain films, needing a change of only 5-10% in bone density to detect lesions. However, lack of specificity may produce false positive results which may result in misdiagnosis. Bone scans may also cause problems when imaging patients with myeloma. Lesions often appear normal or cold, and as such a skeletal survey with plain imaging is of more use (146). Of note is the fact that not all lesions on a bone scan are symptomatic. Many are, and sometimes remain, asymptomatic.

4.3.3 Computed Tomography (CT)

CT scanning is more sensitive at diagnosing bony disease than plain film, but is more cumbersome and expensive for examining the entire skeleton (147). However, it can be helpful to examine soft tissue masses and to clarify which anatomical sites are involved (144). It may also aid identification of the site of the primary lesion.

4.3.4 Magnetic Resonance Imaging (MRI)

MRI is highly sensitive to skeletal metastases, can detect bone marrow abnormalities and allows delineation of the whole spine and identification of spinal cord or nerve root involvement. It can demonstrate lesions that are not apparent on bone scan and is particularly useful in detecting spinal metastases and spinal cord compression. It is the imaging procedure of choice for determining the extent of a lesion, both in skeleton and soft tissues, and is especially useful if surgical intervention is being considered. In some cases MRI may characterise the bony lesion better than plain film and thus may enable a specific diagnosis to be made (145). However, it is less well suited to screening the long bones (144). It also may not be a suitable imaging modality for certain patients. For example, its use is contraindicated in those with pacemakers and claustrophobia. Another disadvantage is that unfortunately MRI often cannot distinguish between changes due to treatment and tumour.

4.3.5 Positron Emission Tomography (PET)

More recently PET has been available. Using fluorodeoxyglucose (FDG), it detects abnormal areas of glucose metabolism in tumour. It is not used routinely to assess bony disease, but has value in oncology to exclude metastatic disease prior to radical treatment, for example in lung cancer. However, it does have moderate sensitivity and high specificity in detecting bone metastases (144).

The radiological investigations described above all have their place in the diagnosis of bony metastases, but evaluation of response to treatment using such techniques is more difficult due to lack of quantitative methods. On plain films, response may be visible as sclerosis, although this can be confused with disease progression. Recalcification of previously lytic lesions only assesses the capacity for bone repair.

It does not measure directly shrinkage of the tumour or reduction in tumour activity (24). On bone scan images, healing lesions usually have less tracer accumulation, although increased uptake may also be seen secondary to the "flare" phenomenon soon after treatment is initiated. Therefore, assessing number of lesions may be a more reliable way to monitor disease response or progression (144). Unfortunately this may still not correlate with the clinical well-being of the patient, and emphasises the fact that relying on one method of assessment may not be optimal.

4.3.6 Additional Investigations

In patients with bone metastases, serum alkaline phosphatase is elevated in 80% of patients with prostate cancer and 40% with breast cancer (24). However, this is not pathognomic for presence of bone metastases. In prostate cancer, PSA is also likely to be high, but this too is not specific for bony disease. Bone biopsy may be necessary to confirm tumour type in cases of unknown primary, especially if this has the potential to alter choice of management. In addition, biopsy may be valuable in cases where all radiological tests are equivocal.

4.4 Pain Evaluation

Pain may be a consequence of an underlying disease process, co-morbidity or treatment. Pain evaluation is vital at multiple stages in a patient's journey. Assessment is required both at the diagnostic stage and also later to evaluate outcome, such as response to interventions. Both assessment of pain in general and in CIBP must be considered.

4.4.1 Assessment of Pain

The long list of published instruments indicates that pain assessment continues to be a challenge. Recommendations have been suggested for the use of pain measurement tools and methods in clinical practice (148). The Expert Working Group recognise that to provide effective pain relief, "requires delineation of the scope of the problem, characterisation of the pain syndromes, determination of optimal therapeutic strategies, identification of barriers to implementation of effective strategies, determination of strategies to overcome these obstructions and the monitoring of outcomes for purposes of continual quality improvement". In theory, this is a sensible and workable strategy, but cancer pain is still often treated inadequately (2). Reasons for poor pain control in this setting have been examined. The ECOG conducted a large, group-wide survey to determine physicians' attitudes and practice in cancer pain management (4). Eighty-six percent of responders felt that the majority of patients with pain were under medicated. Factors identified as reasons for inadequate pain management included patient reluctance to report pain and to take analgesics, concerns regarding side effect management and tolerance, inadequate use of adjuvants, and physician reluctance to prescribe opioids. The study also identified that 31% of physicians would wait until the patient's prognosis was six months or less before choosing maximal analgesia. However, poor pain assessment was felt to be the most important barrier to adequate pain control. Without proper assessment, pain is often underestimated by the health care provider. Lack of a standardised pain assessment tool was a crucial component. This has been shown to be an issue, not only in pain assessment, but also in symptom assessment in general. Kirkova et al. undertook a systematic review to look at cancer symptom assessment instruments (although this did not focus specifically on tools for pain assessment) (149). Twenty-one instruments were identified as appropriate for clinical use, but they varied in their symptom content and psychometric validation. Not one instrument was felt to meet all the criteria for an ideal pain assessment tool. A summary of potential barriers to effective pain management is shown in Table 2.

Table 2. Barriers to pain management

Patient-Related	***Physician-Related***	***Institutional Barriers***
Reluctance to report pain	Poor pain assessment	Lack of time & resources
Concerns about distracting clinician from (cancer) therapy	Knowledge deficit regarding specific treatment for pain	Lack of commitment to make pain treatment a priority
Fear that pain means disease is progressing	Failure to appreciate severity of pain	Lack of use of instruments for pain assessment
Belief that pain must be accepted	Reluctance to prescribe analgesics	Lack of consistent pain management guidelines
Fear of addiction & of being thought of as an addict	Concern about drug regulatory scrutiny	
Worries about side effects	Poor communication	
Fear of tolerance to analgesics		

Studies have looked at the feasibility of quantitative pain assessment in outpatient oncology practice. Rhodes et al. confirmed that pain was common, but pain intensity was rarely assessed quantitatively, often undocumented by the physician and no routine method of assessment was used (150). Using the Visual Analogue Scale (VAS), a simple assessment tool, they then demonstrated that routine pain assessment can be incorporated into oncology practice in an easy and sustainable way.

The general consensus is, therefore, that inadequate pain assessment is one of the most important factors that contributes to poor treatment of pain, and that it should be feasible to provide appropriate pain assessment in practice.

What makes a good pain assessment tool? This question has been addressed by Caraceni et al. (148). The authors summarised a number of criteria that should be adhered to when choosing an appropriate pain measurement tool. The first of these was ease of administration to maximise patient compliance. It may be challenging to balance simplicity of use with the need to gather enough information representative of a patient's pain. This can be particularly problematic in certain circumstances, such as in patients with poor education, or cognitive or communication difficulties. The second fundamental principle recommended by Caraceni et al. was that of validity, to ensure that the instrument "measures what it is meant to measure" (148). This concept was defined by Cook and Campbell in 1979 as "the best available approximation to the truth or falsity of a given inference, proposition or conclusion" (151). It is the statistical reproducibility of a measurement and various ways of testing validity are described. Types of validity include external, internal, construct, criterion and content validity. For example, content validity considers whether a scale has included all the relevant and excluded irrelevant issues in terms of content (152). However, Caraceni et al. point out that because human sensation has no "gold standard" with which to compare, indirect methods of determining validity are required (148). Validity should also be established within the specific area of interest and for multi-cultural use. The tool must also be sensitive to the treatment effect (148). It is important to be able to distinguish between clinically important change and naturally occurring variation. In addition, for specific use in the setting of clinical trials, the instrument used must be appropriate to the study design and intended patient population. However, it should also ideally be generaliseable across patient groups. Other valuable attributes include reproducibility and reliability (24). Reliability is the consistency or repeatability of a measurement or the degree to which an instrument measures the same way each time it is used under the same conditions with the same subjects. It relates to the stability of a measurement, i.e. how far it will give the same results on separate occasions (152). Examples include test-retest reliability (which assesses the stability of the results of a test over time), inter-rater reliability and internal consistency (an estimate of the reliability of a group of questions in a questionnaire to measure the same concept). Care must also be taken to control the environment during assessment so that these factors do not introduce bias (31). For example, the way in which instructions are given or the presence of a spouse may influence performance.

There are different methods of detecting symptoms in both in day-to-day clinical practice and research: chart review, spontaneous reporting and elicitation by survey or questionnaire (153). Volunteered symptoms by spontaneous report may be the most clinically relevant, but may be an underestimation of the situation. Conversely, checklists may suffer with over-endorsement bias in which patients claim multiple symptoms. Homsi et al. examined the difference between symptoms reported by patients after open ended questioning versus those assessed using a 48-question survey in a palliative care setting (154). The median number of volunteered symptoms was one (range 0-6) whereas the median number found using systematic assessment was ten (range 0-25). It seems that there needs to be compromise between a method of assessment which is simple and quick and one which, although more lengthy, provides a detailed understanding of the issues. However, many of the validated assessment tools currently available do not cover all the symptoms and related problems that a patient may experience. It may be that a number of different tools should be used in conjunction to achieve the balance required.

Specifically in pain assessment, it may also help to classify the pain as this may aid in directing further assessment, investigation and treatment strategies. However, several systems are available and they have not been shown to be reliable predictors of cancer pain outcome (138). Examples include classification into acute or chronic pain, organisation according to underlying aetiology or pathophysiology, or as a particular pain syndrome.

It is clear that there are different ways of addressing pain assessment, but as much as possible it is vital that certain criteria are fulfilled to optimise the findings. In some situations, a certain research question may require the use of a uni-dimensional pain measurement tool only. However, pain does not occur in isolation and impacts on functional, emotional, social and spiritual wellbeing. Therefore, in clinical practice an ideal tool should address the problem of total pain as a complex experience with multi-dimensional components. This in itself creates a number of questions; what dimensions should be assessed and how?

In pain assessment, often the first thing that comes to mind is pain intensity or severity. This is typically measured using rating scales such as the VAS, numerical rating scale (NRS) or verbal rating scale (VRS). These scales are all well validated, including in cancer populations, but there are a number of issues to consider (148). The first of these is the scaling properties. A pain measure should start at zero and the distance between the points should be equal, suggesting a linear relationship between pain intensity and report (31). However verbal rating scales may not conform to this principle as the data is categorical and not continuous. Therefore, the difference in intensity between "mild" and "moderate" pain may not be the same as between "moderate" and "severe". In addition, pain intensity may improve, but a patient may still rate it as moderate before and after an intervention, due to the sensitivity of the instrument. Scales with a larger number of choices are more likely to detect change (138).

It is important to assess the temporal characteristics of pain, which may include recency of onset, frequency, and duration of episodes (153). Even with chronic pain it is unlikely that pain remains the same during the day, meaning that the cross-sectional nature of some assessment tools records only a snapshot of the pain at that time and may not be a true reflection of the pain experience (31). This is addressed by questionnaires such as the Brief Pain Inventory (BPI) in which patients rate their pain at its worst, least, average and right now. Because pain characteristics change over time due to changes in the underlying pathophysiology, appropriate frequency of assessment also needs consideration (138, 148).

Although a causal relationship has not been proven, associations have been identified between cancer pain and depression (142). Therefore assessment of the affective component of pain is appropriate. A number of approaches are possible. Validated questionnaires such as the Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Profile of Mood States (POMS) or Centre for Epidemiological Studies Depression Scale (CES-D) may be used and are designed to assess the presence and extent to which someone may be anxious or depressed. However, these are not designed specifically to quantify the effect of pain on mood. As a result, there may be confusion as to whether an answer is a consequence of psychological or physical symptoms (e.g. "I feel as if I'm slowed down"). Alternatively, specific questions in multi-dimensional tools for pain assessment may ask about pain interference with mood (as in the BPI). Another option is to use a questionnaire such as the McGill Pain Questionnaire (MPQ), in which certain descriptors of the pain are classified as an affective dimension, which can then be rated according to severity. Examples of the words available include "fearful" and "punishing-cruel". This combines both qualitative and quantitative measurements of pain. However, it could be argued that has inherent problems. Rating one descriptor as severe would result in the same score as another in which three descriptors were used, but all felt to be mild (31).

Much of the assessment of the sensory aspects of pain stems from subjective report. Certain questionnaires address this, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) or the MPQ. However, certain qualities of pain such as allodynia and hyperalgesia may be evident only by specific testing. Traditional methods of testing sensory nerves, such as nerve conduction studies, assess only large fibres and are unable to measure the presence of positive signs such as allodynia. One method, which allows evaluation of both large and small fibres and sensory gains and losses, is Quantitative Sensory Testing (QST). Its use is discussed later in this chapter.

As with the sensory component of pain, assessment of the functional aspect of pain is often derived from self-report questionnaires. The BPI has questions relating to the degree to which pain interferes with activity, work and walking for example. Similarly, quality of life questionnaires have sections asking about function. Use of performance status to measure function is also widely recognised, but likewise, the assessment is subjective. Ideally, more objective measures of functional outcome are warranted. As with pain assessment tools in general, certain criteria have been specified as ideal requirements for functional assessment in pain management: ease of use; acceptability and familiarity to the patient; requiring a minimum of equipment; reflective of activities performed in everyday life (31). The effect of undertaking a measure of function on the patient's well-being must also be considered. Care needs to be taken when choosing tests of function for additional reasons. Some functional assessments may improve simply by practicing or learning, so that a change may not necessarily be secondary to an intervention. When measuring function it is important to consider the difference between capacity and performance (31). Capacity refers to what is expected physiologically. In reality motivation and cognition contribute. Other factors may influence a functional test, demonstrated by the use of grip strength as an outcome measure in the last chapter. Was this a true measure of function, or was it influenced by fatigue? Pain may also impact on function in numerous ways. Pain may directly result in limited function, but a degree of secondary impairment may result from physical deconditioning, reduced exercise tolerance and muscle wasting (31). It is evident that influences on function may be physiological, psychological, social and environmental and as such it may be difficult to control for the various confounding factors.

Potentially, a wide variety of instruments are available for assessing function in relation to pain. Examples of functional tests used in pain assessment are shown in Table 3. Despite the variety, many are poorly described and standardisation, validity and reliability is lacking. Normative data may not be modified for age and gender, and may not be available at all. Assessing function directly as a measure of outcome is a poorly researched area and further work is vital.

Table 3. Examples of functional tests used in pain research

Function	*Examples of Tests*
Range of motion of painful area	Goniometry
Endurance (fatigability)	Electromyography Sorensen test
Cardiovascular fitness	Treadmill or bicycle ergometers
Timed tests	Walking a fixed distance Stair climbing Sit-ups
Grip strength	Dynamometer

4.4.2 Assessment of CIBP

Rustoen et al. studied a population of patients with CIBP to determine the extent to which pain characteristics, psychological distress, physical functioning, social functioning and quality of life were inter-correlated (5). All of the variables were associated significantly with quality of life. Patients with severe pain had the worst quality of life and depression had the greatest impact. The authors concluded that endpoints of cancer pain studies should include at a minimum, not only measures of various pain characteristics, but also measures of depression, physical functioning and quality of life. As previously described for pain in general, the same principles apply to cancer pain assessment, including CIBP. Thus, evaluation should address the multi-dimensional nature of the pain. However, this is a potentially frail population with deteriorating health, multiple symptoms and co-morbidities, so the assessment needs to take this into account. It may directly influence the process of data collection when pain assessment is part of a clinical trial (148).

A number of specific issues with regards to CIBP assessment have been highlighted.

The main problem is that definitions of pain response to treatment vary, and so comparison between trials is difficult (155). Farrar et al. addressed this issue by determining what levels of change on pain scales represent clinically important differences to cancer patients (not specifically in patients with CIBP) (156). For the percentage of maximum total pain relief and the percentage pain intensity difference, the best cut off point for percentage change was 33%. For absolute pain intensity difference (for scales of 0-10), the best cut off was two. Scales that were converted to a percentage change yielded the best accuracy in predicting adequate pain relief with balanced sensitivity and specificity. Analysis of the proportion of responders in the groups being examined allowed for easier understanding of the clinical importance of the results (157). Using decreases in pain intensity of two points or more or 30% has subsequently been recommended for use in chronic pain trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group (158, 159). This was formed in 2002 to develop evidence-based consensus recommendations for the design and interpretation of clinical trials of treatments for patients with pain, to expedite the evaluations of treatments and facilitate comparisons for study results. These recommendations could be applied to assessment of response to XRT for CIBP. However, because no "gold standard" for pain measurement in this setting existed, the International Bone Metastases Consensus Working Party agreed a set of criteria and endpoints for trials in bone metastases (114, 115). They included the following statements:

- A patient-assessed ordinal pain scale of 0-10 is recommended.
- Patients should have measureable pain (e.g. minimum pain score of 2/10 at time of study entry.
- If studies are designed to assess pain relief for duration of greater than three months, performance status should be an eligibility criterion.
- Measured pain should relate to the worst and average pain for the previous three days at the treated site.
- Opioid analgesics should be converted to daily oral morphine equivalent.
- In addition to pain score and analgesic use, changes in systemic treatment should be recorded.
- A baseline pre-treatment assessment is essential.

- Response rates should be determined at one, two and three months following XRT.
- Complete response is to be defined as a pain score of zero at the treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in daily oral morphine equivalents).
- Partial response is to be defined as either 1) pain reduction of two or more at the treated site on a 0-10 scale without analgesic increase; 2) analgesic reduction of 25% or more from baseline without an increase in pain.
- Pain progression is defined as an increase in the pain score of two or more points above baseline at the treated site with stable analgesic use or an increase of 25% or more in daily oral morphine equivalent compared with baseline with the pain score stable or one point above baseline.

The inclusion of analgesic requirements in response criteria has been debated, and is a difficult issue. It is important to ensure that the pain relief observed is attributable to the treatment being investigated (i.e. XRT), but patients with CIBP often have more than one site of disease. Therefore, when one site is treated it may unmask another painful site, which merits an increase in analgesia. Patients may also require changes in analgesia due to visceral disease or coexisting non-malignant pain. There is not an easy answer for this confounding effect. One point of view is to analyse pain intensity and analgesic requirements as separate endpoints (155). Mercadante suggests the use of an effective analgesic score (EAS) to monitor the analgesic consumption/pain intensity ratio (110). A "run-in" period has also been suggested to aim to optimise treatment prior to the baseline assessment, but this is not a complete solution to the problem (115).

The issue of when to define response after XRT for CIBP was included in the consensus above, but it was not specified if one time point was more appropriate than another. Therefore, Li et al. looked at this question (160). Response rates were calculated at one, two and three months after XRT for CIBP according to the International Bone Metastases Working Group. Response rates varied at the different time points. They concluded that two months after XRT was the most appropriate time to measure response rates for two reasons; 1) maximum pain relief may take more than four weeks to achieve and 2) attrition poses a major problem when response is measured at a later date. In their study only 40% of the original cohort could be reached for follow up at three months.

Another consideration is which pain rating is significant clinically (138). The definitions of response described above do not specify which scale to use if more than one measure is available. Some authors believe that "worst pain" is the best pain to measure, as it is the most relevant in terms of interference with function. Cleeland et al. defined patients as having "substantial pain" if they rated their *worst* pain score as five or more (on a scale of 0-10), as this has been reported to signify disproportionately more functional impairment than scores below five (2). In their study of 1308 outpatients with metastatic cancer, 62% of those with pain were classified using this definition as having pain severe enough to impair function. Serlin et al. also explored the relationship between pain severity and functional interference in cancer patients with metastatic cancer (161). They found three distinct levels of pain severity as defined on a 0-10 numerical scale. Based on the degree of interference with function, ratings of 1-4 were classified as "mild", 5-6 as "moderate" and 7-10 as "severe" pain, illustrating the non-linear relationship between pain severity and functional interference.

Using the worst pain score has been shown to be of value when assessing patients with CIBP. This was demonstrated in a study to characterise CIBP in patients attending the Edinburgh Cancer Centre for palliative XRT (65). Subjects were asked to complete the BPI, MPQ and a BTPQ. Seventy-two patients were enrolled in the study. The results showed that 80% of patients scored their worst pain intensity as being two or more points higher than present pain intensity; felt to be a clinically significant difference in pain severity. This correlated highly with functional impairment. In a separate study by Harris et al., 199 patients with CIBP undergoing XRT were recruited to determine which pain intensity scale in the BPI correlated best with functional interference and should be used to calculate response to XRT (162). One hundred and one patients completed an assessment at baseline and two months after treatment. All pain intensity and functional interference scores for evaluable patients were statistically lower at follow-up. Patients were classified into responders and non-responders according to the International Bone Metastases Consensus Working Party definition. Response rates differed depending on whether the worst, average or current pain score was used. The worst pain score showed the best correlation with functional interference and was felt to be the best measure to use to define response to XRT for CIBP.

Therefore, using criteria suggested by Chow et al. and including measurement of worst pain in CIBP assessment is a sensible step forward (115). Measurement of worst pain provides crucial information on breakthrough pain, which is a particularly troublesome aspect of CIBP to manage. Future research areas for focus outlined in the International Bone Metastases Working Party included quality of life domains such as mobility. Although functional outcomes have been assessed in some studies of CIBP, as described above, these are generally achieved subjectively not objectively. In a review by Wu et al. examining endpoints used in CIBP trials, only four of twelve RCTs examined quality of life (155). One of these used a mobility scale, but this was a subjective measure on a four-point scale (163). At present, there is no quality of life instrument specifically dedicated to measuring functional interference due to CIBP. More direct measures of function have not been examined in this setting. The same can be said for the sensory aspects of CIBP. These are important areas needing evaluation.

In summary, it is important that a comprehensive systematic approach is adopted for pain assessment. This is vital, not only for research purposes, but also to enable a thorough, individualised clinical evaluation in the best interests of the patient. There are a wide variety of options in terms of what and how to measure. In the absence of a gold standard for assessing pain and its effects, it may be preferable to use more than one method of assessment (24). Whatever method is used needs to be acceptable for patients and useful clinically. However, by creating a tool which can assess the multiple aspects of the pain experience, it should be possible to understand the true impact of pain on an individual.

4.5 Assessment Tools used in CIBP Research for my Doctorate

There has been little research done to develop a comprehensive assessment tool to measures the changes in sensation, cognition, mood and function in patients with CIBP. Therefore, this has been addressed in a study outlined in the following chapters. The instruments used were pre-specified in the initial study proposal and therefore were not selected by ACS. However, the choice of tools reflects the issues highlighted above. Some of the measures are in themselves multi-dimensional tools (such as the BPI), but they are used in conjunction with other instruments, with the aim of encompassing all the aspects of pain felt to be important as outcome measures in this setting. The various components included are described below.

4.5.1 Cognitive & Affective Assessment

Visual Analogue Scale (VAS)

The VAS is a commonly used, simple and robust pain measurement tool used to record pain severity and / or improvement. It is usually designed as a 10cm line, with descriptors at each end. The patient marks on the line where they rate their pain severity. The VAS is scored by measuring from the patient's mark on the scale to the beginning of the scale in centimetres.

No pain ____ Worst

0 10 possible pain

There are a number of advantages of using the VAS over other measures of intensity (31). It can be scored quickly providing immediate feedback to the clinician and is reliable, repeatable and sensitive to treatment effects. The VAS provides a quantitative measure of subjective pain experience and is well validated, including in cancer patients (148, 164). Although more frequently used to assess pain intensity, the VAS may also evaluate the multi-dimensional aspects of pain (165). For example, it has been shown to be a useful crude assessment of mood in terminally ill patients with advanced metastatic cancer (166).

The VAS is usually understood well when properly explained. However, care must still be taken, as ease of administration and compliance may decrease in certain situations (e.g. in elderly patients and those with poor education) (138). Such patients may find it hard to conceptualise. Another disadvantage is that there is no consistency in the anchor words in the various VAS tools in the literature or the length of the line used. The VAS functions best for the patient's subjective feeling of pain intensity of present pain or pain right now. It is more limited for assessment of pain in the last week, for example, as memory of pain is not accurate and is often coloured by changing context factors (167). However, it has been shown to be a ratio scale, enabling the quantative expression of pain intensity levels (168). For example, one can conclude that a score of six reflects twice as much pain as a score of three.

Alternative measures which could have been chosen in the current work to record pain intensity include numerical or verbal rating scales. As described earlier in the chapter, a VRS consists of three, four, five or more ranked verbal descriptors such as none, mild, moderate and severe. It is mostly used to measure pain intensity rather than other aspects of pain, such as the emotional impact. It is short, easy to understand and score, and is well understood by patients. However, its restrictive use of words may imprecisely represent the pain experience, and lack of uniformity in the various VRS available means that direct comparisons are difficult (165). A study using simultaneous recordings of pain intensity on VAS, NRS and VRS scales in a large number of patients demonstrated the superiority of the VAS and NRS over the VRS, due to their higher power to detect a difference in pain intensity (169). The verbal categories mild, moderate, and severe pain may correspond to different values on the VAS in the same patient on different occasions, whereas the NRS and VAS values generally agree well (169). Thus, a categorical VRS was not used in the current study. Although perhaps suitable as a coarse screening tool, it was not felt to be accurate enough to detect a change in treatment.

Brief Pain Inventory (BPI)

The BPI is a frequently used, validated multi-item patient-based measure to provide information on pain intensity (sensory dimension), as well as the degree to which pain interferes with function (reactive dimension) (170). It was created by the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care and has been constructed in both long and short versions (171). Since pain can be variable over a day, the BPI asks patients to rate their pain at the time of doing the questionnaire, and also at its worst, least and average over the previous 24 hours. This is measured on a scale of 0 to 10 (0 = no pain and 10 = worst possible pain). To measure pain interference with functionality, the BPI uses seven categories on a scale of 0 to 10 (0 = no interference and 10 = complete interference). Topics include interference with mood, walking, work, social activity, relations with others, and sleep. The BPI asks questions about pain relief, pain quality and the patient's perception of the cause of pain. It also has a figure representing the body to allow the patient to shade the area corresponding to his or her pain.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) have recommended the using the BPI to assess core outcome measures such as pain intensity and physical functioning (158, 159). The BPI has also been studied frequently for use in cancer patients (170-173), is felt to be easy to complete, and repeated administration in a clinical context demonstrated that clinical changes can be detected (148). However, in a survey of pain in patients with advanced cancer, Twycross et al. concluded that the BPI is not brief enough for routine clinical use, but that the short form of the BPI is too short (15). The BPI has demonstrated respectable test-retest reliability over short periods and has been shown to be a valid instrument in cancer patients with bony metastases (172). Recently, Wu et al. verified that the psychometric properties of the BPI were robust in 258 patients with CIBP referred for palliative XRT (174). The Lothian Chronic Pain Service uses it routinely in similar patients. In the research described in subsequent chapters, the Short Form BPI was used, as it was felt to be suitable for the study population when combined with the various other tools (see Appendix). Length of questionnaires may impact on patient compliance, especially if more than one questionnaire is requested.

McGill Pain Questionnaire (MPQ)

The MPQ was developed by Ronald Melzack after his realisation that patients with different pain syndromes use different sets of descriptors and more intense pains are described with more words (175). Initial clinical studies were conducted over a period of five years and were summarised in the first article on the MPQ, which was published in the first volume of the journal Pain in 1975 (176). Since then it has been used widely in research on pain and anaesthetics, and has been used to assess several different types of pain experience (chronic cancer pain (177), chronic lower back pain, venous leg ulcers, tetraplegia, fibromyalgia, rheumatoid arthritis, systemic lupus erythematosis, and labour pain) plus the efficacy of various treatment regimens.

The MPQ is used to quantify a patient's subjective pain experience. It was designed to provide quantitative measures of clinical pain that can be treated statistically. It consists of a series of pain descriptors grouped into classes and subclasses describing different aspects of the pain experience. The descriptors fall into four major groups: sensory, affective, evaluative and miscellaneous. For example, the first class relates to the sensory qualities of pain in terms of temporal, spatial, pressure, thermal and other properties, whereas the second class describes the affective qualities such as tension, fear and autonomic properties (165). The evaluative class contains words that describe the subjective assessment of pain intensity. The subject is requested to chose only the words which best describe their pain experience and to leave out any subclass that is not applicable. The rank value for each descriptor is based on its position in the word set. The sum of the rank values is the Pain Rating Index (PRI). In addition, the Present Pain Intensity (PPI) assesses the pain severity at the time of completing the questionnaire. It is a type of VRS and is based on a categorical scale of zero to five.

Melzack subsequently developed a short form of the questionnaire (SF-MPQ) (178). It contains eleven questions referring to the sensory dimension of the pain experience and four related to the affective dimension. Each descriptor is ranked on a four point intensity scale as 0 = none, 1 = mild, 2 = moderate, 3 = severe to produce the PRI.

The PPI score and the VAS of the standard MPQ are also included in the short form to provide indices of overall intensity. The SF-MPQ correlates very highly with the standard MPQ and recent studies have confirmed its validity (179). The MPQ was developed to indicate the extent of change in pain quality and intensity as a result of an intervention. The SF-MPQ has also been shown to be sufficiently sensitive to demonstrate differences due to treatment at statistical levels (178). Its replicability and consistency have been confirmed in cancer patients (180). However, it has seldom been used to answer clinical research questions in this field.

Deschamps et al. reviewed the benefits and shortcomings of the MPQ (165). Advantages include that fact that numerous studies have investigated its reliability and validity. It has been shown to give consistent results after repeated administration and correlates well with other instruments used to assess the psychological state and pain intensity. However, a number of issues are apparent when considering its use. When the MPQ was originally designed, participants primarily comprised students, the majority of whom were young, male and well educated. Therefore, some of the pain descriptors chosen would not typically reflect those used by patients with chronic pain and may be difficult to comprehend. There is also concern that the questionnaire assumes that pain descriptors within a subclass are equidistant on an ordinal scale. Although the adjectives might be ordered along an intensity dimension, unequal differences may exist between the descriptors. In addition, the sensory dimension contains the most subclasses which means that the relative contribution of the various components of pain may not be adequately reflected when the total score for all classes is calculated. There is no consistency in the number of pain descriptors within each subclass. Pain also has an important cultural background, but translating the MPQ into other languages is difficult (165). Several different language translations are now available, but not for the short-form version.

In the current work the SF-MPQ was used (see Appendix).

Hospital Anxiety and Depression Scale (HADS)

The HADS is a widely used, self-assessment scale comprising statements which the patient rates based on their experience over the past week (181). The 14 statements are relevant to either generalised anxiety (seven statements) or depression (seven statements). The latter are largely composed of reflections of the state of anhedonia. Even numbered questions relate to depression and odd numbered to anxiety. Each question has four possible responses, which are scored on a scale from zero to three. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical "caseness" (the probable presence of a mood disorder).

The HADS has been found to be a reliable instrument for detecting states of depression and anxiety in the setting of a hospital outpatient clinic, with equally good sensitivity and specificity as other commonly used self-rating screening tools. The properties of the scale are robust across a wide spectrum of sub-samples, including groups with somatic problems, mental problems and different strata defined by age, education and gender (182, 183). The anxiety and depression subscales are also valid measures of the severity of the emotional disorder. The HADS was originally developed for psychiatric patients, but it has been validated in cancer patients (184-187).

Although suitable for use in cancer patients, it has been suggested that the HADS performs best in disease-free patients or those receiving active treatment (184). As such, it may be less appropriate as a screening tool for depression in terminally ill patients. There is also an arguement that suggests that alternative cutoff points should be considered in certain populations. There is a lack of consistency with regards to this. Le Fevre et al. concluded that the HADS should be used as a combined scale summing the anxiety and depression sub-scales, rather than the depression scale being used alone. In this way, a combined cutoff score of 20 achieved a sensitivity of 0.77 and a specificity of 0.85, with a positive predictive value of 0.48 (188). Work by Razavi et al. has shown that a combined threshold of 19 had 75% sensitivity and 25% false positive rate for major depressive disorders (186). In this study 210 cancer inpatients completed the HADS and clinical interview. Sixty-two percent of patients had metastatic disease. The high false positive rate was felt to be possibly related to the frequency of acute stress reactions leading to higher distress and higher HADS scores. As a consequence, the authors point out that cutoff scores should be adapted accordingly in inpatient and outpatient settings because hospitalisation is a source of stress which may interfere with psychiatric diagnosis. Lloyd-Williams et al. also showed that a combined HADS total is a more appropriate screen for depression in terminally ill patients than the depression subscale alone (189). In this article, 100 patients with metastatic cancer receiving palliative care with a prognosis of six months or less were interviewed and completed the HADS. The optimum cutoff threshold for identifying cases of depression was 19, which yielded a sensitivity of 68%, specificity of 67% and a positive predictive vale of 36%. The authors speculated that the HADS may over diagnose depression in this population as it is based on anhedonia, and this may be a common feature due to the natural history of disease progression (189). Ibbotson et al. reported various cutoffs for use with the HADS depending on certain circumstances (184). Of a total of 284 patients who completed the HADS, 88 were disease-free, 113 had stable disease and 165 were on treatment. The HADS best identified those patients who had an affective disorder despite being free of cancer, and in this group a combined score of 19 or more gave a sensitivity of 92%, specificity of 95% and positive predictive value of 72%. In patients with stable disease or on treatment, a combined HADS score of 15 or more was best for identifying patients likely to have an interview based diagnosis of depressive or anxiety disorder. A total HADS score of 15 or more has also been used as a level at which to define generally significant emotional distress in cancer patients (190, 191).

Numerous alternative methods of assessing the affective aspect of pain could have been chosen for use in the research presented in this thesis. The choice is difficult as, like pain assessment in general, there are no agreed upon methods on how to assess and classify depression either for research or clinical purposes. The term depression also has different meanings depending on the definition used. For example, it may be defined by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria or may simply be used to reflect distress. In addition, some tools do not take into account duration of affective symptoms and associated functional decline (192). If these factors are ignored, it may be difficult to differentiate normal reactions to certain circumstances and true mood disturbance. Lloyd-Williams et al. reviewed the literature to elucidate which depression tools should be used in palliative care as there are no universally accepted criteria for diagnosis in terminally ill patients (193). The authors highlighted that very few studies have attempted to validate tools for depression in palliative care patients. In the review, only one paper compared the HADS to the "gold standard" psychiatric interview (188). Wasteson et al. conducted a literature review to identify which assessment methods and classification systems have been used in studies of depression in palliative care (192). In the 202 included papers, 106 methods were used for assessing depression / distress. The HADS was used in 76 studies and was therefore the most commonly used assessment method. Other frequently used tools included the Edmonton Symptom Assessment Scale (ESAS), the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the BDI. Use of the HADS dominated in Europe, but was seldom used in Canada or the USA.

Another option which could have been utilised in the current work is a locally developed tool, the Edinburgh Postnatal Depression Scale (EPDS or EDS) (194). It is a 10-item measure originally developed to assess depression in women in the postnatal period. It contains some questions selected from the HADS, excludes the somatic symptoms of depression and includes questions relating to subjective sadness, hopelessness, guilt and thoughts of deliberate self harm over the previous seven days. Each question is rated on a four point scale with a maximum score of 30. It has subsequently been validated in patients with advanced metastatic cancer (195). The authors felt it was an appropriate tool to use in this setting, as studies of other instruments have focused on patients with early disease or patients undergoing active treatment, rather than the terminally ill. They showed that the three items in the EDS that are derived from the HADS loaded negatively onto a separate factor in factor analysis, suggesting that these items may measure a different construct of depression (195). In addition, they demonstrated higher sensitivity and specificity of the EDS than the HADS in patients with advanced metastatic cancer. However, in other work, the EDS and the HADS appear to be similar in terms of sensitivity, specificity and positive predictive value (193). When compared with the single question "are you depressed?" and a verbal mood rating scale, the EDS was the most reliable instrument for detecting clinical depression in palliative care patients (196). A brief, abbreviated version of the EDS has subsequently been shown to be more discriminating for depression in patients with advanced cancer than the original 10-item version (197). A shorter questionnaire has the advantage of not requiring patients to be well enough to concentrate for long periods of time.

On particular issue with assessment of affect in patients with chronic pain is the overlap which exists between symptoms attributable to physical disease and those due to anxiety or depression. This is especially challenging in palliative cancer patients in which symptoms such fatigue, poor appetite, weight loss and sleep difficulties can be explained by disease, treatment and by low mood (192). Different methods are used to overcome this issue. Some questionnaires have been designed for use in physically ill populations and so exclude somatic depressive symptoms. Endicott proposed that the somatic symptoms should be substituted for non-somatic symptoms in the patient with cancer (198). However, if this has not been taken into account the prevalence of depression may be inflated and include those subjects with normal sadness. This may be an issue in the HADS questionnaire, with specific questions such as "I feel as if I am slowed down" (question 8), although it was designed for use in medically ill patients with exclusion of somatic symptoms. Lloyd-Williams et al. highlighted this by showing that question 8 was scored highly by most palliative patients completing the HADS and as such it is a universally poor discriminator for depression in this setting (189). Guidelines have now been formulated for depression in patients with comorbid medical illness in general (199).

It is often unclear why a specific measure is selected for use in research suggesting that the choice of assessment method is often made out of habit rather than on clear theoretical grounds (192). This may be an appropriate criticism of the current work. Although tools were chosen to compliment each other to allow a comprehensive evaluation of the various apects of CIBP, familiarity to the Lothian Chronic Pain Service may have influenced the preferences in assessment methods. Despite this, the HADS was felt to be an appropriate choice in view of its general strengths. Although it has been shown to be too complex for hospice inpatients (200), it was the opinion of the investigators that predominantly out-patients with CIBP in this study would find it acceptable. The original cutoff points for anxiety and depression were used as other thresholds are not universally accepted. The questionnaire is included in the Appendix.

Fear and Avoidance of Pain Scale (FAPS)

Fear avoidance models have been proposed in the literature to describe how specific psychological factors may be associated with pain intensity, physical impairment and disability (201). As a consequence, a number of instruments have been developed for assessment purposes such as the Fear Avoidance Beliefs Questionnaire (FABQ) (202), the Fear of Pain Questionnaire (FPQ) (203) and the Fear and Avoidance of Pain Scale (FAPS) (204). The majority of studies in the literature using these tools involve chronic back pain, rather than cancer-related pain. However, the FAPS is routinely used by the Lothian Chronic Pain Service in cancer patients, and therefore experience suggested it was an appropriate scale to use in the current research. It is easy to administer and quick to complete. It consists of 21 items and shows good internal consistency and temporal stability, is sensitive to treatment changes and relates to other measures in an understandable way (204). The questionnaire is included in the Appendix.

Pain Catastrophizing Scale (PCS)

Catastrophizing has been defined as an exaggerated negative orientation towards pain stimuli and pain experience (205). Catastrophizing is felt to be an important predictor of pain and disability in patients with pain and is associated with a heightened pain experience. Sullivan et al. suggested that catastrophizing, as measured by the PCS, has three related components: rumination ("I can't stop thinking about how much it hurts"), magnification ("I worry that something serious may happen") and helplessness ("There is nothing I can do to reduce the intensity of the pain") (206). The PCS consists of thirteen items describing different thoughts and feelings that individuals may experience when they are in pain (see Appendix). Patients are asked to reflect on past painful experiences and to rate them on a five point scale ranging from zero (not at all) to four (all the time). Questions one to five and twelve reflect helplessness, questions six, seven and thirteen reflect magnification, and questions eight to eleven measure rumination. The three subscales are assessed and a total score is calculated. The factor structure, reliability (including high test-retest correlation) and validity of the PCS have been documented and it has shown to have excellent internal consistency (207).

Studies have been done in various chronic pain groups to assess whether certain components of catastrophizing are more predictive than others. In patients with soft tissue injuries, catastrophizing, as assessed by the PCS, was correlated significantly with patients' reported pain intensity, perceived disability and employment status, with the rumination subscale as the strongest predictor of pain and disability (208). A similar study investigated the relationship between pain catastrophizing and neuropathic pain, and whether there was a different association between spontaneous and evoked pain in this regard (209). In this group of patients, the PCS and the SF-MPQ were utilised. The results showed that the total PCS was correlated significantly with the severity of pain symptoms associated with spontaneous neuropathic pain. The total PCS also correlated significantly with the affective subscale of the SF-MPQ, but not with the sensory subscale. The helplessness dimension of catastrophizing was found to be associated most strongly with the experience of spontaneous neuropathic pain. No association was found with evoked pain. These studies demonstrate the PCS to be a useful tool by adding to the understanding of psychological influences on the experience of pain. They also suggest that by learning which factors contribute to the pain experience, this may help to tailor interventions for pain. The authors suggest that by assisting patients to avoid excessive focus on their pain sensation, this may be a viable means of reducing catastrophizing in a manner that may facilitate rehabilitation.

Unfortunately, the studies above do not include cancer patients. In this group of patients, catastrophizing has been studied to a small degree, but little has been done using the PCS. However, a study by Bishop and Warr demonstrated the usefulness of the PCS when examining coping and catastrophizing in a group of women with breast cancer (210). Patients had either chronic pain related to cancer or cancer treatment and completed a number of self-report instruments including the BPI and HADS. Twenty-eight percent of the women had bone pain primarily. They confirmed the suggestion that catastrophizing may be an important area to assess in cancer patients with pain in order to help targeted management.

It is also worth considering whether the PCS is actually measuring a true catastrophizing state or in fact a patient trait. This is purely speculative, and until questionnaires such as the PCS are more commonplace and further work is done in this area, this question will remain unanswered.

4.5.2 Sensory Assessment

Quantitative Sensory Testing (QST)

QST is a well recognised and widely used method of assessment in pain clinics. It is routinely used by the Lothian Chronic Pain Service, including in those patients with CIBP. It is simple to carry out and is tolerated well by patients. It is a psychophysical test requiring alert patients who understand fully the given instructions and are capable of cooperating during the assessment. In theory, it uses clinical signs to reflect the underlying pathophysiology and augments the traditional neurological examination. However, it is not a diagnostic test for one specific disease entity, but aids in the mechanism-based diagnosis of pain (211). The assessment gives profiles of somatosensory function for two body areas, one affected site and a normal control (ideally the equivalent dermatomal region on the contralateral side of the body), which can be used to infer the possible abnormality.

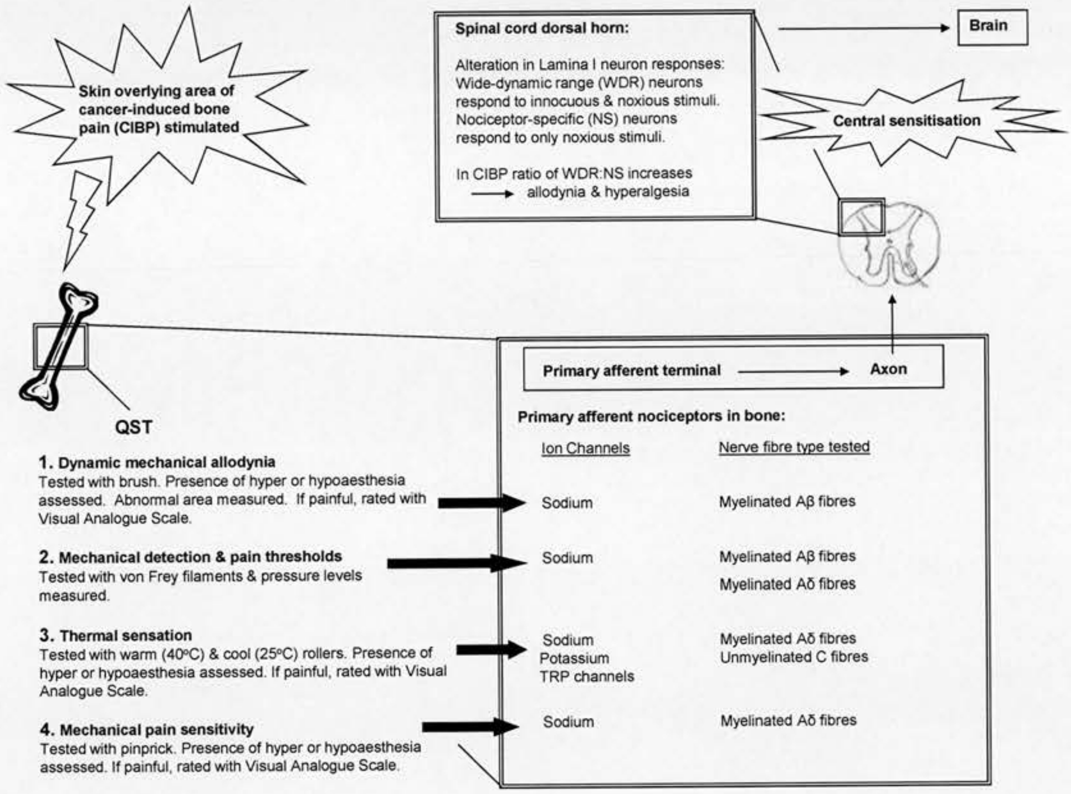
QST was first described by Fruhstorfer in 1976 when a quantitative method was used for the examination of thermal sensibility (212). It uses quantified sensory stimuli to assess the response in a quantitative manner (213). However, it can also provide qualitative data. Its use in the characterisation and assessment of pain relies on what we know about the plasticity of the nervous system. As described in Chapter 2, tissue and nerve injury induce peripheral sensitisation of nociceptors, which may lead to hyperexcitability of the dorsal horn and subsequent central sensitisation (214). These phenomena can be detected with QST. For example, injury may cause normally non-painful sensation transmitted via Aβ fibres to become painful (allodynia), and this can be detected using a calibrated brush. When sensitised, nociceptors cause a barrage of input via Aδ and C fibres and primary hyperalgesia to mechanical and thermal stimulation may be detected using a combination of tools such as von Frey filaments, pins and thermal rods. Central sensitisation may also be detected, for example, with an assessment of wind up. Modality specific sensory dysfunction can be evaluated in this manner. The nerve fibres tested by QST are summarised in Table 4 and a simplified outline of the potential neurobiological basis of QST testing in CIBP is shown in Figure 5.

Table 4. Nerve fibres tested with QST

QST Parameter	*Nerve Fibre Tested*
Dynamic Mechanical Allodynia	Aβ
Vibration	Aβ
Mechanical Detection Threshold	Aβ
Mechanical Pain Threshold	Aδ
Cool Stimuli	Aδ
Warm Stimuli	C
Mechanical Pain Sensitivity	Aδ
Wind up (Temporal Summation)	Aδ

Although there is general agreement in the theory behind QST, no standardised paradigm exists and methodology varies widely. This was demonstrated in a review by Shy et al. in 2003 (215). The instruments used can range from simple handheld tools to computer assisted systems of examination. An example of the latter is the CASE IV system, which has been used by Gruener and Dyck (213, 216). This is an automated device for detecting and characterising sensory thresholds, which quantifies the threshold by administering stimuli according to a test algorithm and records the response for analysis. However, the modalities tested only include vibration and thermal parameters. Previous versions also tested touch pressure, but this was omitted subsequently, due to complicated instrumentation and long testing time (and the fact that vibratory thresholds can be substituted as a measure of large fibre function). Currently the literature is unable to confirm superiority of one QST instrument over another (217).

Figure 5. The neurobiological basis of QST



Rolke et al. published a thorough approach to assessment of QST (218). In this work, the German Research Network on Neuropathic Pain (DFNS) aimed to characterise the somatosensory phenotype of patients with neuropathic pain to help understand the underlying mechanisms. They implemented a protocol to establish age and gender matched reference values for QST parameters in 180 normal subjects. The protocol gave a profile for one region within 30 minutes, with the full profile taking an hour. The assessment was performed bilaterally over the face, hands and feet and comprised the following parameters:

- Thermal detection thresholds for perception of cold, warm and paradoxical heat sensations.
- Thermal pain thresholds for cold and hot stimuli.
- Mechanical detection thresholds for touch and vibration using von Frey filaments and a 64Hz tuning fork.
- Mechanical pain thresholds (pin prick and blunt pressure).
- Stimulus / response functions for pin prick and dynamic mechanical allodynia (standardised brush).
- Pain summation to repetitive pin prick stimuli (wind up).

Subjects were also asked to give a pain rating for each stimulus. In summary, the protocol comprised seven tests measuring 13 parameters. Tests were always performed in the same order, by trained staff using the same equipment (in each participating centre) with standardised instructions for participants. All observers were trained by the same instructor. Using this paradigm, Rolke et al. found that some QST parameters were region specific and age dependent. Sensitivity was higher in the face than the foot. Subjects ≥ 40 years were significantly less sensitive than younger subjects for all QST parameters. Most thermal and mechanical thresholds increased with age. Pain thresholds were lower in women than in men, but detection thresholds were independent of gender. Dynamic mechanical allodynia was not seen in healthy subjects. There were no significant differences in parameters between the right and left sides of the body. The results also suggested that right and left comparisons (relative reference data) may be up to 2.5 times more sensitive to detect positive (i.e. hyperalgesia) or negative (i.e. hypoaesthesia) sensory signs than comparisons with absolute reference data. This is of relevance to the studies described in subsequent chapters. However, if comparisons were made between different body regions (rather than right and left), then no advantage was seen with the use of relative reference data. In their research, Rolke et al. were able to produce evidence for the use of a z-score to allow sensory profiles to be displayed. In this score, each individual parameter is related to its region, age and gender specific reference range and is displayed as the number of standard deviations above or below the normal mean (218). Following development of their protocol, Rolke et al.

successfully tested its practicality in 18 healthy subjects (211). Further data from the DFNS, discussed at the British Pain Society Annual Scientific Meeting 2007, suggested no major differences between inter-observer and test-retest reliability.

There are a number of different approaches to QST assessment in terms of the parameters measured and the tools used. In addition, there are various methods of stimulus presentation (213, 215, 219, 220). These are classified depending on whether subject reaction time is included in the measurement, and are known as reaction time inclusive or exclusive. Threshold values obtained by the former are usually higher and more variable than those obtained by the latter, which is a more time consuming method (215, 219). An example of a reaction time inclusive technique is the method of limits. This involves gradually increasing the stimulus to the point of detection or reducing the stimulus intensity to the point of disappearance (or a combination of both). The changing levels of intensity can be gradual or in a stepwise fashion, and can be specified in absolute intensities or in units of "just noticeable differences" (JNDs). An example of a reaction time exclusive algorithm is the method of levels (or forced choice). In this method, stimuli of defined intensity levels are tested with the subject indicating whether a specific level is detected. Therefore, the stimulus intensity is determined depending on patient response. There are also a variety of methods of response to a stimulus. An example of this is the yes-no paradigm, in which a stimulus may or may not (a null stimulus) be present. The subjects must correctly identify the stimulus event 50% of the time, and if the patient answers yes to the null stimulus too frequently, then reassessment and further instruction may be necessary (213). All of these methods can be influenced by performance and have their advantages and disadvantages with regards to sensitivity, specificity, reliability and ease of testing (219). Therefore, Gruener and Dyck stress that for any modality evaluated, the events must be described in detail and validated adequately (213).

Another issue to consider is patient comfort, as discussed by Stubhaug (214). As can be seen from the work described above, sensory and pain thresholds are an integral part of QST. Some evidence suggests that suprathreshold stimuli may provide a more sensitive measure of treatment effect. However, this type of stimulation has the potential to evoke longer-lasting increases in pain, which may be unacceptable to patients.

Although the specifics of QST measurement vary, there are a number of issues on which a general consensus exists, such as the environmental conditions required for testing (213, 215). For example, the subject should be assessed at an ambient temperature, in a quiet and comfortable setting. The background conditions during stimulus administration should be kept as constant as possible. The patient should be alert and given a uniform set of instructions. To further reduce error, the patient can be asked to look away or close their eyes during testing and the use of null stimuli may assess their cooperation. Increasing the degree of automation of the testing should reduce bias between tests. The same equipment should be used and this should be periodically calibrated. Ideally, normative data should be available so responses can be compared, but they can only be used if the exact conditions used by the authors are replicated (215, 219). If used in patients in a clinical setting rather than healthy volunteers, it is also important to interpret the results in conjunction with the clinical presentation (217). QST should not be the sole criteria used in diagnosis of disease, and other appropriate tests should be utilised (215).

Since the first publication (212), QST has been used increasingly in both day-to-day clinical practice and research. Gruener and Dyck suggest a number of settings in which QST may be advantageous (213). These include: studies that evaluate normal sensory function or its recovery and the role of various parameters as covariates in determining sensory perception; epidemiological studies of both normal and patient or disease cohorts; evaluation of the effects of treatment; evaluation of small fibre dysfunction; further classification of hypersensitivity phenomena with the aim of finding the cause. QST may also be useful to complement other measures of sensory nerve fibre function.

QST now has a role in the diagnosis of disease, staging, follow-up and assessment of treatment. Its clinical utility has been examined in a review of 350 articles by Shy et al. in a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (215). QST has been of particular value in the management of diabetic neuropathy and its use is now recommended in this setting. Approximately 50% of diabetics have polyneuropathy and thermal abnormality may be the earliest pathology in its development (219). Evidence suggests that QST is an effective tool for documenting vibration and thermal thresholds and for longitudinal evaluation of diabetic neuropathy (215). It has also been used to examine neuropathy secondary to vitamin deficiency, uraemia, alcohol abuse, carpal tunnel syndrome, human immunodeficiency virus (HIV), infection, trauma, cerebrovascular disease, central nervous system disorders (such as multiple sclerosis and syringomyelia) and autoimmune disease (215, 219, 220). QST has grown in popularity for assessment of neuropathy, but it has also been used to examine pain syndromes (221), such as post-herpetic neuralgia (222), painful diabetic neuropathy (223, 224) and radiculopathy secondary to lumbosacral disc disease (225). Ziegler at al showed that large and small fibre function in the feet was worse in those with painful diabetic neuropathy than those who were painfree (223). Results by Kramer et al. contradict this finding, although the authors did find a correlation between thermal threshold and intensity of pain (224).

Although the use of QST is well established in some areas of medicine such as diabetes, evidence for its use in cancer patients is limited. In 1987, Lipton et al. assessed vibration thresholds in the upper limb to assess large nerve fibre function in 171 cancer patients and 58 healthy controls (226). There was a significant difference between the groups, with 12% of cancer patients with elevated thresholds versus only 1.7% of controls. The authors speculated that this may be related to the malignancy rather than known risk factors for neuropathy. In 1991, the same team used QST to assess the prevalence of sensory nerve dysfunction in cancer patients with a variety of tumour types, but also included a test of thermal threshold to determine small fibre function (227). QST was performed in 29 cancer patients and 100 healthy controls. Those with any identifiable risk factors for neuropathy were excluded. Vibration and thermal thresholds were assessed in the non-dominant index finger and big toe. No relationship was seen between type of malignancy and sensory thresholds. Mean vibration and thermal thresholds were elevated significantly in the toes, but not the fingers of cancer patients. Elevated vibration thresholds were found in the toes in 31% of cancer patients and 6% of control subjects. For thermal thresholds, the rates were 43% and 4% respectively. Large fibre sensory dysfunction, as identified by QST, was present (in fingers and / or toes) in 37.9% of cancer patients and small fibre dysfunction was seen in 50% of patients. Again, these findings were felt to represent a neuropathy, directly or indirectly, associated with cancer.

A number of authors have used QST in the setting of chemotherapy-induced neuropathy in cancer patients. For example, Chaudhry et al. used QST as part of the neurological evaluation in a study to measure the neurotoxic effects of cisplatin and paclitaxel chemotherapy in 21 cancer patients (228). After treatment, vibratory thresholds increased above baseline in the great toe in 81% of patients and in 52% at the index finger. The elevations in thresholds correlated with the cumulative taxol dose. Elderson et al. examined vibration and thermal thresholds in 20 women with advanced ovarian cancer receiving cisplatin-based chemotherapy (229). Vibration threshold, but not thermal threshold, was elevated during treatment. Forsyth et al. undertook a study to characterise and quantify paclitaxel-induced peripheral neuropathy in 37 women with metastatic breast cancer and to determine the utility of QST (230). Twenty-six percent of patients with symptoms had a painful neuropathy. They concluded that, although QST quantified the neuropathy, it did not predict subclinical neuropathy, and was less sensitive than clinical examination. More recently, Caraceni et al. used QST (including tests of thermal sensation, pin prick and vibration thresholds) along with nerve conduction studies to investigate the pathophysiological features and temporal relationships of paclitaxel peripheral neuropathy in women with breast cancer (231). Binder et al. used the DFNS QST protocol (in conjunction with the MPQ) to demonstrate a characteristic somatosensory profile of cold, heat and mechanical hyperalgesia in painful neuropathy secondary to oxaliplatin in patients with gastrointestinal cancer (232). Vincristine-induced pain was shown to be associated with dysfunction of Aβ, Aδ and C primary afferent fibres using QST (233).

Another use of QST in cancer patients was in a study by Reznikov et al., in which it was used to explore differences in pain sensitivity in patients with malignant (n=75) and non-malignant (n=149) pain using either opioid or non-opioid analgesics (234). Although no significant differences were found between the analgesic groups, QST appeared to be a useable tool in this setting.

QST has been utilised in animal models of CIBP (42-45, 52, 54, 56, 57). In murine models, measurement of mechanical allodynia can be done by assessing behaviour such as paw withdrawal after von Frey filament or electronic anaesthesiometer stimulus. In a similar manner, cold allodynia can be evaluated with a drop of acetone. However, the use of QST in patients with CIBP appears to be an innovative application.

QST has a number of advantages over tests such as standard electrophysiology. Firstly, it is simple to perform and is tolerated well by patients. Whereas electromyographic nerve conduction studies can only assess large myelinated fibres, QST can assess sensory loss in both large (tactile thresholds) and small fibres (thermal thresholds), as well as sensory gains (hyperalgesia, allodynia and hyperpathia) (235). Laser-evoked potentials can assess small fibres, but are insensitive to sensory gains. QST can be used in conjunction with other tools in a complementary manner to provide the required assessment.

A disadvantage of QST is that it requires significant patient cooperation and the effects of non-organic factors on the results are not fully known. Although the physical stimuli are objective, because it requires patient interaction, it has a subjective component (215). It tests the entire somatosensory pathway, but it cannot locate an abnormality at a specific level (213). In addition, although it can evaluate specific classes of sensory fibre, QST may not always be able to infer the aetiology of the sensory pattern. There are not many contraindications to use, but accurate testing would be potentially difficult in those patients with skin conditions. QST may also be time consuming. The DFNS protocol, although comprehensive, takes an hour to complete both test areas (211, 218). Although the authors conclude that this is a “short form QST battery”, certain patient groups may find it too lengthy and time constraints are a reality in clinical practice. Their protocol includes tests that were not felt to be necessary for the purposes of the studies in subsequent chapters. In our research, the small number of tests required could be performed in a short timeframe, acceptable to the patient, and still provided information on all the primary afferents (Aβ, Aδ and C fibres). This may be relevant particularly for frailer cancer patients in whom minimising the number of potentially unpleasant stimuli would be advantageous. When choosing which QST parameters to assess, it is also important to decide the question which needs to be answered. For example, is it is necessary to be able to differentiate a deficit of small or large fibre function? The tests required may vary depending on whether QST is being performed by the bedside, in the laboratory or as part of a clinical trial. There may also be disadvantages intrinsic to the tools themselves. An example of this is seen with traditional synthetic plastic von Frey filaments which can be susceptible to changes in temperature and humidity, and hence need frequent recalibration. One solution is to use filaments made of optical glass fibres (236). QST does not assess small fibres associated with autonomic nerve function. For this, investigations such as cardiovascular autonomic reflex testing and quantitative sudomotor axon reflex testing (QSART) are available. The latter test uses sweat response to measure small fibre function, and in a study by Tobin et al., it was found to be a more sensitive measure of small fibre dysfunction than QST (237).

The varying methodology used in studies of QST result in limitations when comparisons are required. The issue of examiner variability also brings criticism. In addition, comprehensive data are lacking on the reproducibility, sensitivity and specificity of QST. These problems need to be addressed with further standardisation of the methodology of pain research. Work is required to compare QST devices and to evaluate the results against other neurological tests. This needs to be coupled with longitudinal studies to help characterise specific pain syndromes and disease with a view to gaining more understanding of the effects of treatment (including analgesics) on QST. Increasing knowledge of the underlying mechanisms of pain with QST may lead to the development of novel therapies.

QST was used to assess the sensory aspects of CIBP in the studies described in subsequent chapters. The following methods were used:

Dynamic Allodynia with Brush Testing

Firstly, the painful area was mapped and marked out on the skin if there was abnormal sensation. The area of abnormal sensation was measured and recorded in mm^2. Dynamic mechanical allodynia was assessed using a standardised calibrated brush (Somedic, Sweden) stroked over a length of skin bilaterally. The patient was asked to describe how this sensation compared with the control area (hyperaesthesia, hypoaesthesia or unchanged) and, if painful, it was rated with the VAS of zero to ten as already described. The control area chosen was the equivalent dermatomal region on the contralateral side of the body. For midline spinal sites of CIBP, an alternative painfree spinal level was used as the control area.

Mechanical Sensation

Mechanical detection threshold (MDT) was determined at the painful and control sites using a standardised set of von Frey nylon filaments (Somedic Aesthesiometer, Sweden). They constitute a series of 17 filaments of varying thickness, calibrated according to the force to make them bend. The force required to buckle the monofilament increases from 0.026g in the first handle in the set to 110g (corresponding to a pressure range of $1.7g/mm^2$ to $137.3g/mm^2$). Specifications for the monofilaments are shown in Table 5. A consistent amount of pressure can be elicited by pressing the filament against the skin perpendicularly for two seconds to produce 3-5mm of bowing. The filaments were tested in ascending order (i.e. using the method of levels technique) and the detection level noted when felt consistently at a certain force (detecting three out of five applications). Mechanical pain threshold (MPT) was assessed using the same filaments and the force noted at the level the stimulus became unpleasantly prickling or sharp. The pain intensity was rated using the VAS. Suprathreshold level was measured as the fibre which was felt as the most uncomfortable (i.e. the highest tolerable fibre), and was also rated with the VAS. Mechanical pain sensitivity (hyperalgesia) was tested in both areas using pin prick stimulus (Neurotips™ Owen Mumford). Lastly temporal summation (known as wind up) was assessed. For this, a train of pin prick stimuli of the same force was given within a small area at a rate of 1/second. For both pin prick and wind up the patient was asked to give a pain rating. This allowed calculation of the wind up ratio (WUR). This is calculated as the VAS rating of the wind up stimulus divided by the VAS rating of the single pin prick stimulus. It reflects a frequency dependent increase in excitability of spinal cord neurons and pain.

Table 5. Specifications for von Frey monofilaments

Hair Number	*Nominal Force (g)*	*Pressure (g/mm2)*
3	0.026	1.7
4	0.034	2.3
5	0.064	2.9
6	0.085	3.3
7	0.145	4.5
8	0.320	6.8
9	0.390	7.3
10	1.10	14.1
11	1.70	17.5
12	3.30	25.0
13	5.10	31.6
14	8.30	39.1
15	17	57.8
16	24	72.5
17	34	84.4
18	50	96.1
19	110	137.3

Thermal Thesholds

Using warm and cool rollers (Somedic Rolltemp) in both the affected and control areas, the presence of hyperaesthesia or hypoaesthesia or thermal allodynia was examined, and rated with the VAS. The rollers were set at 40°C (eight degrees above normal skin temperature) and 25°C (seven degrees below normal skin temperature). Abnormalities in thermal sensation and thermal hyperalgesia can reflect nerve damage or peripheral and central sensitisation. Temperatures of 40°C are frequently suprathreshold for pain, but are unlikely to produce anything other than mild or transient discomfort for patients.

In the studies in Chapters 6 to 9, one major advantage was that all the QST assessments were performed by one trained examiner (ACS) in exactly the same order. Therefore, the issue of examiner variability was not a concern in this work.

4.5.3 Functional Assesssment

GAITRite Electronic Walkway

Gait analysis is a useful tool, although subjective analysis has poor to moderate reliability and validity. Objective assessments are more reliable and valid, but are time consuming, expensive and need expertise. One solution is an instrumented walkway such as the GAITRite electronic walkway, which is quick to use, needs little expertise, and is being used increasingly to evaluate treatment efficacy and function. The GAITRite system is a computer-based, instrumented walkway that measures spatial and temporal gait characteristics (Tables 6 and 7). The roll up walkway comes in various lengths with embedded pressure sensors. It assesses multiple aspects of gait simply by walking along the walkway placed along the ground. Data is uploaded onto a computer and automatic footstep identification and parameter calculations are done providing quantitative information. The current research used a 14-foot mat.

Table 6. Spatial GAITRite parameters

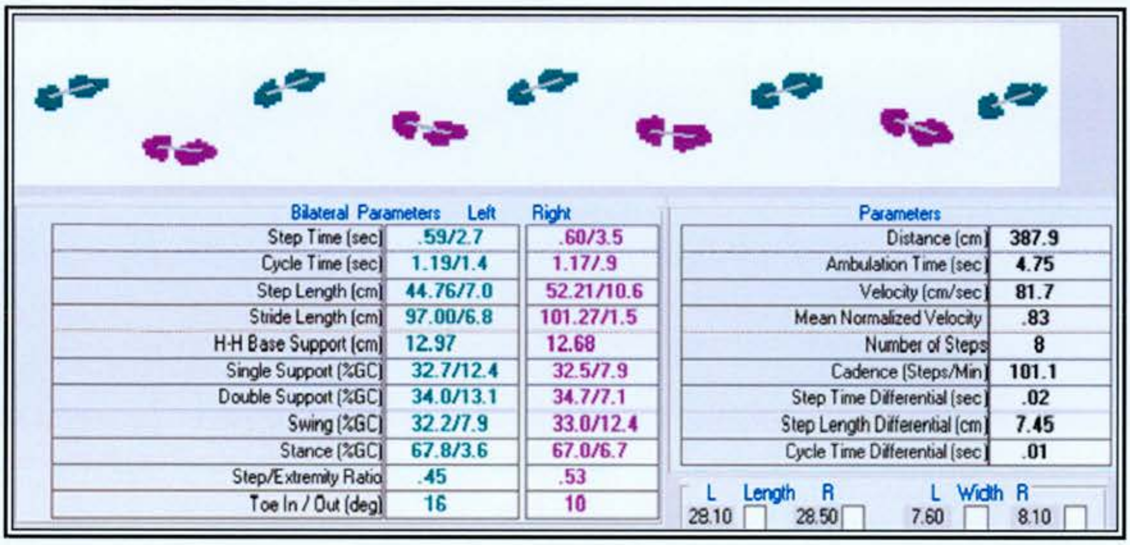
Spatial Measurement	***Definition***
Distance (cm)	Measured on the horizontal axis from the heel centre of the first footprint to the heel centre of the last footprint.
Line of Progression	Line connecting the heel centres of two consecutive footfalls of the same foot.
Leg Length (cm)	Measured from the greater trochanter to the floor .
Stride Length (cm)	Distance between the heel points of two consecutive footprints of the same foot.
Step Length (cm)	Measured from the heel centre of the current footprint to the heel centre of the previous footprint on the opposite foot.
H-H Base of Support (Base width) (cm)	Vertical distance from heel centre of one footprint to the line of progression formed by two footprints of the opposite foot.
Toe In / Toe Out (degrees)	Angle between the line of progression and the midline of the footprint.
Cadence (steps/min)	The number of steps per minute.

Table 7. Temporal GAITRite parameters

Temporal Measurement	*Definition*
Ambulation Time (sec)	Time elapsed between first contact of the first and last footfalls.
Step Time (sec)	Time elapsed from first contact of one foot to first contact of the opposite foot.
Gait Cycle (GC) Time (sec)	Elapsed time between the first contacts of two consecutive footfalls of the same foot.
Velocity (cm/sec)	Obtained after dividing the distance travelled by the ambulation time.
Mean Normalised Velocity (leg length/sec)	Obtained after dividing the velocity by the average leg length.
Single Support (%GC)	Time elapsed between the last contact of the current footfall to the first contact of the next footfall of the same foot. Expressed as a % of gait cycle time.
Double Support (%GC)	The time when both feet are on the floor. Expressed as a % of gait cycle time.
Stance Time (%GC)	Time elapsed between the first contact and last contact of two consecutive footfalls on the same foot. Expressed as a % of gait cycle time.
Swing Time (%GC)	Time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot. Expressed as a % of gait cycle time.

In addition to the parameters above, the Functional Ambulation Performance (FP) score is calculated by the system. This was developed by Nelson in 1974 as a single score of gait to measure objectively the efficacy of treatment (in hemiparetic training) (238). A scoring system was created using published human locomotion data, and is based on the ratio of step length to leg length to step time. Also factored into the score are bilateral asymmetries. For more detailed gait analysis, as well as sensing the geometry of footprints, the walkway can sense the relative arrangement between footprints in a two dimensional plane and the relative vertical component of pressure exerted by each footprint. It also allows testing in those subjects with ambulatory aids such as crutches or walking sticks. A normal range has been built into the system extracted from documented peer-reviewed scientific literature and the GAITRite database, so that each parameter is classified as being within or outside of the normal range. Examples of data that can be collected are shown in Figures 6 and 7.

Figure 6. An example of GAITRite data collected for one walk

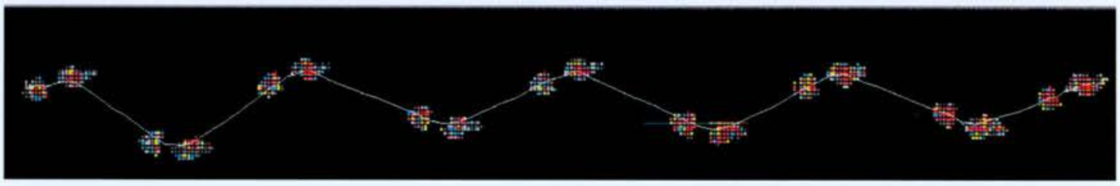


Bilateral Parameters	Left	Right
Step Time (sec)	.59/2.7	.60/3.5
Cycle Time (sec)	1.19/1.4	1.17/.9
Step Length (cm)	44.76/7.0	52.21/10.6
Stride Length (cm)	97.00/6.8	101.27/1.5
H-H Base Support (cm)	12.97	12.68
Single Support (%GC)	32.7/12.4	32.5/7.9
Double Support (%GC)	34.0/13.1	34.7/7.1
Swing (%GC)	32.2/7.9	33.0/12.4
Stance (%GC)	67.8/3.6	67.0/6.7
Step/Extremity Ratio	.45	.53
Toe In / Out (deg)	16	10

Parameters	
Distance (cm)	387.9
Ambulation Time (sec)	4.75
Velocity (cm/sec)	81.7
Mean Normalized Velocity	.83
Number of Steps	8
Cadence (Steps/Min)	101.1
Step Time Differential (sec)	.02
Step Length Differential (cm)	7.45
Cycle Time Differential (sec)	.01

Length L	Length R	Width L	Width R
28.10	28.50	7.60	8.10

Figure 7. An example of footfall analysis



The parameters used depend entirely on the aims of the gait analysis. The outcome will also vary depending on the instructions given to participants. For example, in work addressing the validity and reliability of the system, subjects were asked to walk at self-selected pace, fast pace and slow pace (239). A set of guidelines have been developed by the European GAITRite Network which was established in 2003 (240). The consensus on data collection includes general advice on environmental conditions, safety issues and measurement procedures.

The GAITRite walkway has been used widely in numerous patient groups including the frail elderly (241), stroke patients (242, 243), patients with Parkinson's disease (244-246), patients with peripheral arterial disease (247), orthopaedic populations (248), and in children (249). It has also been used for assessment in individuals with Alzheimer disease (250) and progressive supranuclear palsy (251). Applications in these groups include assessment and reduction of falls, study of the effectiveness of gait training, rehabilitation and research. In many of these settings, the walkway has been shown to have good to excellent validity, reliability and test-retest reliability (239, 252-254) and is a good instrument to evaluate treatment effects (244). It appears that utilising the GAITRite Electronic Walkway to assess gait in cancer patients, in particular those with bony pain, is a novel use. It is reasonable to assess mobility in patients with CIBP, as movement-related pain is characteristically problematic. This may provide a useful, objective assessment of function in this population.

activPAL Ambulatory Physical Activity Meter

The activPAL ambulatory physical activity meter (PAL Technologies Ltd) was used to measure general function. This is a reusable, single unit device, requiring no calibration that records step number and instantaneous cadence for each period of walking. In addition, the monitor classifies an individual's free-living activity into periods spent sitting or lying, standing and walking. It can be used to estimate daily energy expenditure (see below) for weeks and gives a "real-life" measure of functional impairment. It is small (5.3 x 3.5 x 0.7cm) and weighs 20g. It is simple to wear and is secured easily to the anterior thigh with hypoallergenic adhesive pads or similar dressing. It is not felt to interfere with day-to-day activities. The activPAL uses an accelerometer to sense movement coupled with offline algorithms to generate the activity record. The device has substantial processing capacity and memory, allowing activity and posture to be recorded continuously for periods of up to fourteen days on a second by second basis. It interfaces via a USB connection with a Windows compatible computer with software allowing the data to be presented in various ways consistent with the needs of the user.

Examples of data which can be obtained from the activPAL are shown in Figures 8-12.

Figure 8. An example of a 24 hour activPAL recording

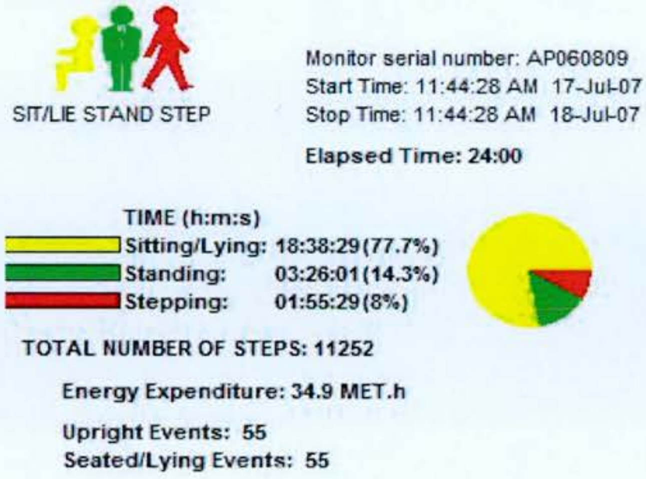


Figure 9. An example of data presented by the day

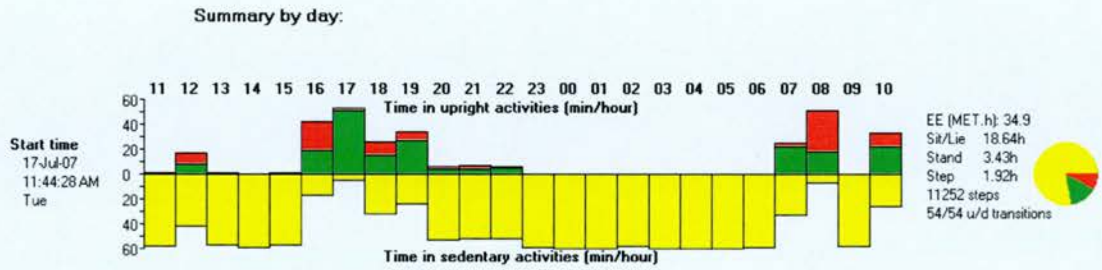


Figure 10. An example of data presented by the hour

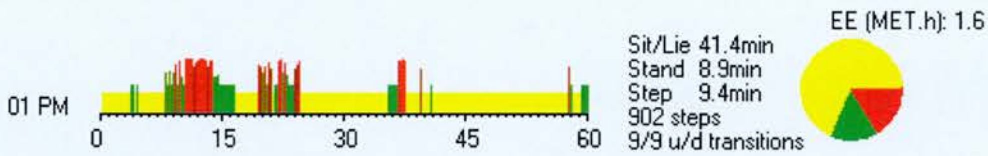
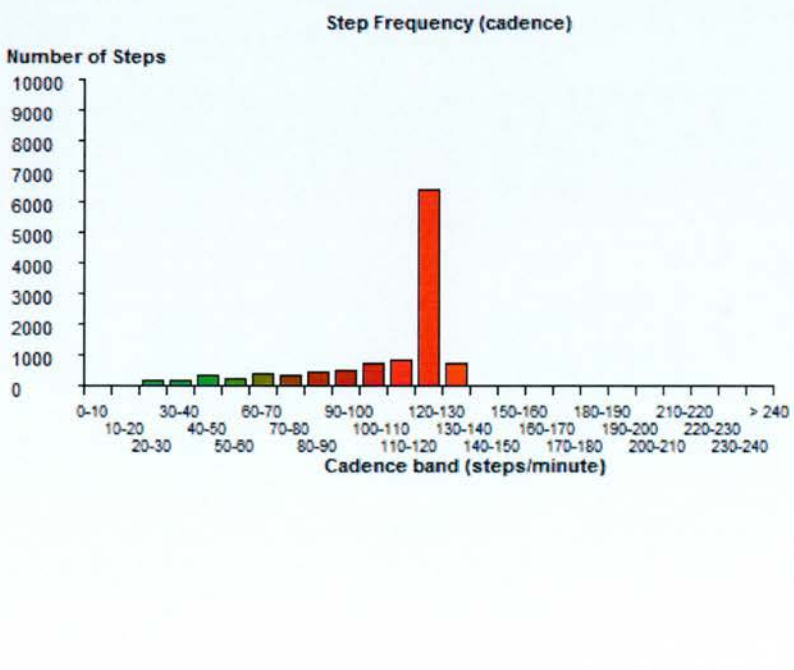
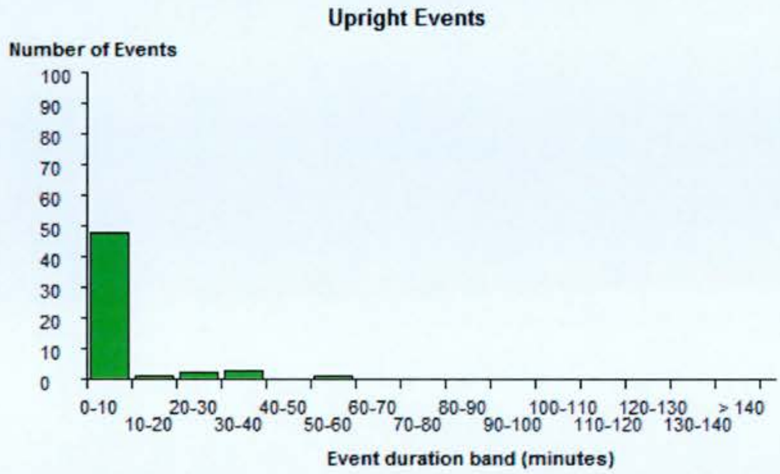


Figure 11. An example of a graph showing frequency of cadence in 24 hours



Most frequent cadence during this period was 120-130 steps/min.

Figure 12. An example of a graph showing standing duration in 24 hours



Most upright events (standing) lasted less than 10 minutes.

Energy expenditure can be estimated with the activPAL. This is possible because when the meter classifies the day into sitting/lying, standing and stepping, each is given a "metabolic equivalent" (MET) value, reflecting the estimated energy cost of that activity. These values are derived from a table of measured values (255). A MET represents the ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1kcal/kg/hour and is roughly equivalent to the energy cost of sitting quietly. Sitting/lying and standing have fixed values of 1.25 and 1.4 MET respectively. The value for stepping is scaled with increasing cadence. Total energy expenditure is given in MET/hour which equates to approximately 1kcal/kg. Sitting/lying only for 24 hours would give a MET/hour of 30 (i.e. 24 hours x 1.25 MET) and therefore this is the lowest energy expenditure recordable.

Using the activPAL has significant benefits over the use of a device such as a waist worn pedometer. Pedometers display cumulative step number, but give no indication as to when in the day the wearer was active, how long each walk lasted or the intensity. Additionally, accuracy is compromised by slow walking speeds and obesity. Potentially, this would result in serious limitations in a frailer group of users such as this study population of patients with CIBP. The activPAL has been shown to be a valid and reliable measure of walking, and the accuracy is not influenced by walking speed (256). Similarly, it has been demonstrated to be a valid and reliable measure of posture and motion (257). However, these studies were performed in healthy adults, and very short duration walking activities were more difficult to classify. Another disadvantage is the relatively high cost when compared to a waist-mounted pedometer. This can be balanced by the quality and detail of the information provided.

The activPAL has previously been used to assess limitation in function due to fatigue and weight loss in cancer patients. In a study by Dahele et al., 20 patients with advanced upper gastrointestinal malignancy receiving palliative chemotherapy were compared with age-matched healthy controls to compare physical activity (258). The research also explored the relationship between patients' activity, quality of life and clinical performance status. The study indicated that it was practical to objectively measure free-living physical activity in patients with cancer using advanced ambulatory technology and supported use of the activPAL meter as a patient-centred, functional endpoint in oncology.

ECOG Performance Status

Performance status (PS) in the third trial is measured with the Eastern Cooperative Oncology Group (ECOG) performance scale rather than the KPS. Published by Oken et al in 1982, the score runs from zero to five with zero equating to perfect health and 5 denoting death (259). It has also been called the WHO or Zubrod score and is shown in Table 8.

Table 8. ECOG Performance Status

Grade	*ECOG*
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self care. Totally confined to bed or chair
5	Dead

4.6 Conclusion

A vital component of pain management is a comprehensive assessment, which should include the basic principals of clinical history taking, physical examination, diagnostic investigation and pain evaluation. A major barrier in this process is the lack of a comprehensive pain assessment tool, which takes into account key aspects of pain, such as sensation, cognition, mood and function. In patients with CIBP, these issues are particularly important to optimise quality of life. This chapter has outlined a variety of tools which may be of use in this setting. Their value in the assessment of CIBP before and after treatment will be examined in subsequent chapters.

Chapter 5 THE VALUE OF QST IN CIBP ASSESSMENT

5.1 Introduction

As discussed in previous chapters, the gold standard treatment for CIBP is palliative XRT (8). However, the analgesic effect is not immediate and 50% of patients may not get a good analgesic response (7, 112). There is not currently a diagnostic test or marker that will predict those likely to benefit from XRT, nor are the analgesic mechanisms of XRT understood fully. Recently developed animal models of CIBP show that the underlying neurobiological changes associated with CIBP are unique and different from both inflammatory and neuropathic pain (39), with evidence that some of these changes can be reversed by XRT (260). By attempting to link symptoms and clinical signs with mechanisms, using techniques such as QST, it may be possible to target treatment strategies more effectively, as has been proposed for neuropathic pain (261). Further research in these areas is vital to aid in the discovery of predictive markers and the development of novel targeted treatments for CIBP. Such biomarkers would potentially contribute to delivery of individualised management with major clinical benefit.

It is clear from reviewing the literature that little research has focused on the sensory aspects of pain assessment. QST is a widely recognised tool for sensory evaluation, although much of the work has focused on diseases such as diabetes and neurological disorders. It has been used less in cancer research and mainly in relation to chemotherapy-induced neuropathy. Pain syndromes have been examined, but not particularly in relation to malignancy. Therefore, the next step in the research agenda is to explore whether QST can be used to characterise clinically the sensory aspects of CIBP. In addition, it is important to establish the effects of treatment on these sensory measures and whether this can be used to predict response to XRT. This chapter describes preliminary research which explores the potential value of using QST in this setting. Two hypotheses were examined:

1) The mechanisms of CIBP can be identified with QST?
2) QST parameters change following an analgesic response to XRT?

5.2 *Method*

5.2.1 Study Population

Patients with CIBP attending the Edinburgh Cancer Centre were recruited to two small pilot studies (Table 1), with the common aim of further characterising malignant bone pain. Patients were identified on attendance at the outpatient clinic or via screening of oncology medical notes and the XRT diary on a daily basis. After ethical approval and written informed consent, patients with CIBP from any primary tumour site, scheduled to receive palliative XRT, were recruited. For inclusion patients had to meet the following criteria: diagnosis of malignant bony metastases, supported by histological or radiological investigations; presence of CIBP; aged 18 years or over at study entry; aware of the current stage of cancer and its implications for prognosis and treatment. Subjects were excluded from participating if they met any of the following criteria: unstable or rapidly deteriorating clinical condition; presence of spinal cord compression or any other medical or psychiatric condition that would confound the objectives of the study; inability to complete the study assessments; and patients who would be adversely affected by study participation. The ethical and R&D approval letters, patient information sheets and consent forms for both pilot studies are included in the Appendix.

5.2.2 Study Assessments

In the first pilot study, patients completed the short form BPI and QST prior to receiving XRT for their pain. In the second study, patients completed the same assessments before XRT and also 4-6 weeks after treatment. Standard demographic data were collected along with analgesic use. Twenty-four hour morphine equivalent dose was calculated using standard conversion tables (262). Both the BPI and QST have been described in Chapter 4. In this work the paradigm for QST was still being refined and as such the method varied slightly from that in subsequent research (Chapters 6-9). In the pilot studies, the following QST parameters were recorded: area of abnormal sensation; brush sensation (& VAS); mechanical detection and pain threshold with von Frey filaments; suprathreshold level (& VAS); pin prick sensation; thermal sensation (& VAS). In view of the fact that suprathreshold level and corresponding VAS score was used to determine mechanical pain sensitivity, a VAS score was not required as part of the pin prick testing. Wind up was an additional measure not utilised until later work.

5.2.3 Statistical Analysis

Analysis (Minitab® 15 Statistical Software) included descriptive statistics for demographics and the Wilcoxon signed rank test for comparisons between the CIBP and control site, and differences before and after XRT. The Mann-Whitney test was used to compare responders and non-responders. The analysis looked at all patients completing the study as one group, followed by examination of the characteristics of those who gained a clinically significant analgesic response to XRT. A responder was defined as having a ≥30% reduction in total BPI score, which has been shown to be significant clinically (156-159). A p-value of less than 0.05 was considered statistically significant. As a large amount of data is described, significant findings will be highlighted in red in the current and subsequent chapters.

5.3 Results

5.3.1 Hypothesis: The Mechanisms of CIBP can be Identified with QST?

5.3.1.1 Demographics

Seventeen patients were recruited to the first study and their data combined with the data for those recruited to the second study (n=28). Of these 45 patients, 20 (44%) were male and 25 (56%) female with a median age of 66 (range 33-83) years. Twenty patients were seen on the inpatient wards of the cancer centre and the remainder assessed on an outpatient basis. All had a diagnosis of metastatic malignancy to bone and had CIBP. Eighty percent of patients had a primary diagnosis of breast (19 patients), prostate (11 patients) or lung (6 patients) cancer. Other primary sites included renal, colon, head and neck, myeloma and unknown primary. The main site of CIBP was most commonly the lumbar spine.

5.3.1.2 Analgesic Use

Analgesic use was recorded for all patients during the previous 24 hours. Both regular and as required medications were documented. Forty-three patients (96%) were using analgesia of some variety for their bone pain. Thirty-five patients (78%) were taking regular weak or strong opioid medication. Fourteen patients (31%) had required no opioid breakthrough medication in the prior 24 hours. Median total morphine equivalent dose over the previous 24 hours (available for 28 patients) was 26mg (range 0-300mg). Thirty-five patients (78%) were taking non-opioid based analgesia. Nineteen of these patients used only one type of non-opioid medication. However, seven patients required two preparations, seven were prescribed three preparations and two patients used four non-opioid drugs in combination. Numbers of patients taking each type of non-opioid analgesic are shown in Table 9. In summary, 35 patients were using a total of 62 non-opioid medications.

Table 9. Non-opioid analgesic use

Non-opioid preparation	*Number of patients*
None	10
NSAID	17
Paracetamol	21
Gabapentin	10
Amitriptyline	2
Lignocaine Patch	3
Ketamine	1
Steroid	8

5.3.1.3 BPI Results

In the 45 patients, median scores (range) for "pain right now", "average pain" and "worst pain" were 4 (0-8), 5 (2-8) and 8 (4-10) out of 10 respectively. As part of the BPI, the 43 patients using analgesia were also asked what percentage relief their pain medications had provided in the prior 24 hours, with zero representing no relief and 100%, complete pain relief. Median pain relief was 70% (0-100%). Results of the seven interference scores are available for 28 patients and are shown in Table 10.

Table 10. BPI functional interference scores

Pain Interference with:	*Median (out of 10)*	*Range*
General activity	5.5	0-10
Mood	5	0-9
Walking ability	5	0-9
Normal work	6.5	0-10
Relations with others	0.5	0-8
Sleep	5	0-10
Enjoyment of life	6	0-10
Total score (out of 70)	34.5	4-61

5.3.1.4 QST Results

Brush

An area of abnormal sensation (median size 1350mm^2, range 170-92600mm^2) was elicited with brush testing in 24 (53%) of the 45 patients. Of these 24 patients with altered sensation, 15 had increased sensation to brush testing and nine had reduced sensation. Sixteen of the 45 patients (36%) had pain with brush testing (dynamic mechanical allodynia). The median VAS in these 16 patients with dynamic mechanical allodynia was four (range 1-8).

Mechanical Sensation

Three parameters were assessed as previously described: mechanical detection threshold, mechanical pain threshold and suprathreshold. For each of these, values were recorded for the test area with CIBP and a normal control. Median pressures exerted in each area are shown in Table 11. The measurements are presented as the pressure exerted by each filament (g/mm^2).

Table 11. Median von Frey pressures at CIBP and control sites

	Median Pressure in CIBP Area (g/mm^2)	*Range*	*Median Pressure in Control Area (g/mm^2)*	*Range*	*P value*
MDT	6.8	1.7-31.6	7.3	2.3-25	0.503
MPT	25	4.5-57.8	17.5	6.8-57.8	0.047
Suprathreshold	137.3	17.5-137.3	137.3	31.6-137.3	0.008

When measuring MDT, 18 patients (40%) demonstrated increased sensitivity (lower detection threshold) and 15 patients (33%) had reduced sensitivity in the CIBP area (higher detection threshold) when compared with the control area, although the difference was not significant statistically. However, MPT was significantly different between the CIBP and control sites with 19 patients (42%) with lower thresholds and 10 (22%) with higher thresholds. Median (range) suprathreshold VAS was two (0-9) at the CIBP site and zero (0-10) at the control site, with a median difference of one ($p=0.001$). Mechanical pain sensitivity (hyperalgesia), tested with pin prick in 27 patients, showed that 13 patients (48%) had normal sensitivity, but 12 (44%) had increased and two (7%) had reduced sensitivity to this stimulus.

Thermal

At the CIBP site, increased warm sensitivity was found in 26 of the 45 patients at baseline (58%), of whom 19 patients rated this as painful. Reduced warm sensitivity was found in five of 45 patients (11%), of whom none rated it painful. Median VAS to warm stimulus was zero (range 0-9) at the CIBP site and zero (0-2) at the control site, but the difference was significant ($p<0.001$). Increased cool sensitivity was found in 24 patients (53%), of whom 16 patients rated this as painful. Reduced cool sensitivity was found in 2 of 45 patients (4%), of whom none rated it painful. The difference in VAS to cool stimulus between the CIBP and control site was also significant ($p<0.001$). Nineteen patients (42%) had increased sensation to both warm and cool stimulus. Only 11 patients (24%) had entirely normal thermal sensation. The QST results are summarised in Table 12.

Table 12. Summary of QST results: CIBP site in comparison with control

	Normal Sensation (same as control)		**Abnormal Sensation at CIBP Site**			
			Increased sensation		**Reduced sensation**	
	No	%	No	%	No	%
Brush	21	47	15	33	9	20
MDT	12	27	18	40	15	33
MPT	16	36	19	42	10	22
Suprathreshold	28	62	14	31	3	7
Pin prick	13	48	12	44	2	7
Warm	14	31	26	58	5	11
Cool	19	42	24	53	2	4

These findings were discussed by the author in an oral presentation at the 5th Research Forum of the EAPC in Norway in May 2008 (see Appendix) (263).

5.3.2 Hypothesis: QST Parameters Change Following an Analgesic Response to XRT

5.3.2.1 Demographics

Twenty-three patients (a sub-group of the 45 patients described above) underwent both pre and post XRT assessments. The group comprised 13 men and 10 women with a median age of 73 (range 33-83) years. The most common primary diagnoses comprised breast (35%) and prostate (39%) cancer. Eighty-three percent of patients (19/23) were seen as outpatients pre-treatment and all were outpatients at follow up.

5.3.2.2 BPI Results

Overall pain improved significantly after XRT. Table 13 shows the changes in total and worst BPI scores along with the functional interference subscale pre and post XRT. Median 24 hour morphine equivalent dose reduced from 25mg (range 0-215mg) pre XRT to 20mg (0-320mg) after XRT, but the difference was not significant (p=0.27). Thirteen out of 23 patients (57%) had a clinically significant analgesic response to XRT. In these patients, total BPI score improved by a median 42 compared to a median reduction of one for non-responders (p=0.0002). In responders, no significant change in opioid dose was seen after XRT (p=0.722). Similarly, the difference in non-responders was not significant (p=0.281).

Table 13. Median (range) BPI scores before and after XRT

	All patients n=23			Responders n=13			Non responders n=10		
	Pre XRT	**Post XRT**	**P value**	**Pre XRT**	**Post XRT**	**P value**	**Pre XRT**	**Post XRT**	**P value**
Worst Pain	8 (4-10)	5 (0-9)	0.001	8 (5-10)	3 (0-9)	0.003	7.5 (4-10)	7.5 (4-8)	0.37
Functional Interference	32 (4-61)	21 (0-43)	<0.001	32 (4-61)	7 (0-28)	0.002	33.5 (7-42)	30.5 (2-43)	0.17
Total BPI	65 (27-110)	48 (10.5-100)	0.001	65 (38-110)	31 (10.5-64)	0.002	68.5 (27-88)	63.5 (27-100)	0.62

5.3.2.3 Effect of XRT on QST

Pre-XRT 8/23 (35%) patients had abnormal sensitivity to brush stimulus of whom five responsed to XRT. In the responders, abnormal sensitivity to brush normalised in 3/5 patients and the area of abnormal brush sensation reduced from a median of 9750 (range 775-92600) mm^2 to zero (0-6575) mm^2 ($p=0.059$). In non-responders, sensation remained abnormal and the area of abnormal sensation reduced from 2550 (1350-13125) mm^2 to 1662 (525-23100) mm^2 ($p=1.00$). Two patients had resolution of dynamic mechanical allodynia (one responder and one non-responder).

Differences were seen after XRT with von Frey filaments. When all patients were analysed as one group, median MDT at the CIBP site was 7.30g/mm^2 pre and post XRT, but the difference was significant ($p=0.036$). MPT increased from a median (range) of 25 (6.8-57.8) g/mm^2 to 31.6 (3.3-96.1) g/mm^2 after treatment ($p=0.001$). When patients were classified depending on their response to treatment, thresholds increased after XRT in both responders and non-responders for MPT, but only for MDT in non-responders (Table 14). The suprathreshold level was 137g/mm^2 for all patients both before and after XRT with a median VAS of 1 (range 0-8).

Table 14. Median (range) MDT & MPT before and after XRT at CIBP site

	Responders n=13			Non-responders n=10		
	Pre XRT	**Post XRT**	**P value**	**Pre XRT**	**Post XRT**	**P value**
MDT	7.3 (1.7-31.6)	7.3 (2.9-57.8)	0.91	7.05 (3.3-14.1)	14.1 (6.8-39.1)	0.022
MPT	25 (6.8-57.8)	31.6 (3.3-96.1)	0.028	15.8 (7.3-31.6)	28.3 (14.1-84.4)	0.011

Prior to treatment, abnormal sensitivity to warm, cool and pin prick stimulus was found in 14/23 (61%), 10/23 (43%) and 12/22 (55%) of patients respectively. Sensory changes were also noted in these parameters after XRT (Table 15). In responders to XRT, warm allodynia resolved in one patient. In non-responders, three cases of warm allodynia resolved, but in one patient it was increasingly painful. No responders had cool allodynia, but one non-responder rated pain to cool higher after XRT.

Table 15. Thermal & pin prick sensation: response after XRT

		Responders n=13				Non-Responders n=10			
		Pre XRT	Post XRT			Pre XRT	Post XRT		
			No change	AbN to N	N to AbN		No change	AbN to N	N to AbN
Warm	Normal	6	6	-	0	3	2	-	1
	Abnormal	7	2	5	-	7	6	1	-
Cool	Normal	7	6	-	1	6	5	-	1
	Abnormal	6	2	4	-	4	2	2	-
Pin Prick*	Normal	7	7	-	0	3	3	-	0
	Abnormal	6	2	4	-	6	3	3	-

* n=13 for responders, n=9 for non-responders; N=normal; AbN=abnormal

An association was found between resolution of altered heat perception and response to treatment. Differences were noted between those who had normalisation of abnormal warm sensation ("warm normalisers", n=6) in comparison with other patients (n=17), who had either no pre-existing abnormality of warm sensation or where abnormal warm sensation remained abnormal after XRT. These warm normalisers had higher baseline functional interference BPI scores, larger reductions in pain scores (functional interference & total BPI) and a higher percentage responded to XRT as shown in Table 16.

Table 16. Changes in BPI scores depending on thermal response to XRT

		"Warm Normalisers"	All other Patients	P value
Median Worst BPI score:	**Pre XRT**	8	8	0.55
	Post XRT	5.5	5	0.94
	Median difference	3.5	2	0.57
Median Functional BPI score:	**Pre XRT**	43	31	0.0389
	Post XRT	22	19	0.75
	Median difference	29	6	0.0156
Median Total BPI score:	**Pre XRT**	72.5	63	0.13
	Post XRT	43	54	0.55
	Median difference	45.5	12	0.0273
% patients with analgesic response to XRT		83%	47%	-

Also, proportionally more warm normalisers (50%) had reduced size of the abnormal area with brush testing after XRT compared with only 24% of other patients. Similarly, proportionally more warm normalisers (50%) had resolution of hyperaesthesia to pin prick after XRT compared with only 19% of other patients. These results were presented in poster format by the author at the IASP 12^{th} World Congress in Pain in Glasgow in August 2007 (see Appendix) (264).

5.4 Discussion

The first hypothesis was "the mechanisms of CIBP can be identified with QST". We addressed this by amalgamating two pilot studies allowing the sensory characteristics of patients with CIBP to be examined. This showed that more than half of patients had altered sensation to brush testing and over one third of patients experienced this as painful. This demonstrates that the normally non-noxious large myelinated Aβ fibres are functioning abnormally in CIBP. Seventy-three percent of patients with CIBP had altered mechanical detection thresholds and 64% had altered pain detection thresholds with von Frey testing suggesting dysfunction of both Aβ and small myelinated Aδ fibres. Statistically significant differences were seen between the CIBP and control sites for MPT, suprathreshold pressure and the mechanical pain severity. Thermal sensation was also found to be abnormal. Altered warm sensitivity was documented in 69% and altered cool sensitivity in 58% of patients. Pain ratings secondary to warm and cool stimuli were also significantly higher at the CIBP site than the control area. Thus, small unmyelinated C fibres are also damaged as shown by abnormal temperature response. Such findings demonstrate the plasticity of the nervous system after tissue and nerve injury as a consequence of both peripheral and central sensitisation (214). The data also confirmed that CIBP has an impact on functional activities and mood as shown by the BPI. It is clear that patients can have significant pain despite analgesic polypharmacy.

Despite being associated with increased morbidity, anxiety and depression and reduced performance and quality of life, CIBP is a neglected area of research. The current sensory findings have not previously been described clinically and indicate that there are unique changes underlying the pathophysiology of CIBP. We already know from animal models that there are fundamental differences between this and purely inflammatory and neuropathic pain. Changes seen in primary afferents and the spinal cord with inflammatory pain, such as increases in SP, CGRP and protein kinase C, and changes with neuropathic pain (for example decreases in SP and CGRP and increases in galanin and NPY), were not seen with CIBP (42). Luger et al. also demonstrated that in the mouse model, the doses of morphine required to block bone cancer pain-related behaviours was ten-fold greater than with inflammatory pain (53).

Our current QST paradigm comprised brush, von Frey, thermal and pin prick testing, but did not assess the presence of wind up. This temporal summation is seen in neuropathic pain models. It is induced by constant C or Aδ fibre stimulus with deep dorsal horn neurone responses dramatically increasing despite a steady input into the spinal cord. Wind up needs a certain frequency of stimulation to produce its effects, but can augment responses of dorsal horn neurones by twenty times in amplitude and may prolong responses after cessation of peripheral input (265). Testing could be added to the current QST protocol to assess whether this is a feature of CIBP, to improve characterisation in future studies. This is done in the subsequent study.

The first analysis in this chapter focused on characterising the sensory components of CIBP prior to treatment with palliative XRT. The next hypothesis was that "QST parameters change following an analgesic response to XRT". To explore this, patients were classified as responders and non-responders to XRT for CIBP. An analgesic response was seen in 57% of patients, which confirms what is already known about the likelihood of benefit of this treatment (116, 266). In these patients, worst, functional interference and total BPI scores significantly improved. Changes in the sensory characteristics of CIBP in response to XRT were demonstrated. These included a reduction in the size of the area with abnormal brush sensitivity, as well as alterations in other parameters of mechanical sensitivity – both noxious and innocuous. In a proportion of patients, abnormal responses to thermal stimulation resolved, with an association between those patients with altered heat perception and response to treatment. In patients who had resolution of abnormal sensitivity to warm stimulus after XRT, there was a suggestion that they had higher baseline pain scores, larger reductions in pain scores and were more likely to have an analgesic response to treatment.

These sensory findings, in particular the thermal results, may have implications in the development of a tool to predict response to XRT for CIBP. Biomarker research in this area is important for a number of reasons. In the research presented in subsequent chapters, it was seen that approximately 30% of patients were not fit enough to complete a pain assessment approximately two months after palliative XRT. However, survival has not been thoroughly examined as an endpoint in research looking at XRT for CIBP. The attrition rate seen in this study population may also be an underestimation, as those patients eligible to take part in trials may be a fitter sub-group of those with CIBP. Also of note, is the fact that half of patients who get complete relief of pain after XRT take more than four weeks to achieve it (7). In frailer patients, with poor performance status or limited life expectancy, being able to predict response to treatment would enable an informed choice as to whether a single fraction of XRT is warranted, especially as this still requires attendance at a specialist centre that may be some distance away for the patient. In addition to rewards for patients with targeted treatment, health economic costs may also benefit from being able to predict response to treatment. This may be of particular value in countries where the organisation of services is not streamlined with coordinated medical and clinical oncology healthcare provision.

The management of CIBP with XRT has been extensively reviewed, but research has not focused on biomarkers as predictors of response to treatment. Instead it has mostly investigated optimal fractionation schedules (112, 113, 116, 267-269). One paper did examine prognostic variables as well as fractionation, and found that the initial pain score and site of the primary lesion were important prognosticators (7). Patients with prostate and breast primaries had more frequent complete pain relief than those with lung and other primaries. These findings have not been evident in similar studies. Hoskin et al. examined the use of urinary markers of bone resorption (pyridinoline and deoxypyridinoline) as a possible biomarker of response (270). An association was seen between relief of CIBP and low marker concentrations before and after XRT suggesting that osteoclast activity could be a predictor for pain response. Despite this finding, no consistent clinical biomarkers of response to XRT are known.

The use of QST to assess changes in somatosensory perception before and after treatment has been demonstrated in the non-malignant setting. In patients with osteoarthritis, reversal of abnormal sensory findings was seen when pain was treated successfully (271). In painful diabetic neuropathy, it has been suggested that the intensity of pain can be predicted by thermal thresholds as a measure of small nerve fibre dysfunction (224). Using QST to assess both large and small fibre sensory dysfunction has also been utilised in cancer patients (227), but its use to assess sensory changes in response to treatment in this setting is novel. However, it does appear to be of value in this preliminary research in patients with CIBP. The altered thresholds to mechanical and thermal stimuli seen with QST, demonstrates the increased activation, heightened responsiveness and plasticity of primary afferents. We have also shown reversal of allodynia, hyperalgesia and reduction in the size of the sensitive area (receptive field) after XRT. Thus, QST may be detecting alteration of peripheral neuronal mechanisms, but in addition, it may be eliciting signs as a consequence of changes in the dorsal horn. Immunohistochemistry from animal models has shown that the dorsal horn undergoes significant modulation prior to processing by higher centres (41, 42). Such changes mean that spinal cord neurons, that are normally only responsive to noxious stimuli, also become responsive to non-noxious stimuli. The various proportions of these nociceptive specific (NS) and wide-dynamic range (WDR) neurons in lamina I have been shown to alter in CIBP, paralleling the development of hyperalgesia and allodynia (44, 45). Validation of this use of QST is needed in larger appropriately designed trials.

The use of palliative XRT trials for biomarker development has recently been examined and the ethics debated (272). Despite being a potentially vulnerable population, so long as the principles of informed consent are adhered to and patients understand fully the aim and burden of the study, it seems reasonable for them to take part in such research. The potential population is large and quick recruitment may be feasible if trial entry has fewer restrictions. Wan et al. suggest that these palliative patients provide a potentially valuable resource to facilitate the discovery and validation of biomarkers predictive of radiation response and toxicity (272).

However, an ongoing issue is the wide variation in methods used to measure bone pain. Variations in the site and extent of bony metastases, in the primary cancer and other interventions such as analgesics, mean that the precise contribution from XRT is difficult to assess accurately. Trials come to different conclusions depending on which definitions and endpoints are used. As described in the previous chapter, this has been discussed by the International Bone Metastases Consensus Working Party and areas of agreement and conflict have been addressed (114, 115).

5.5 Conclusion

Further study of CIBP and XRT needs to be high on the research agenda in a time when targeted, individualised care for cancer patients is a priority. The selection process for deciding which patients should receive treatment needs refinement. Both patients and health economics may benefit from being able to predict which patients respond to treatment. This study has suggested that patients with CIBP, with resolution of altered sensitivity to warm thermal stimulus after XRT, have larger reductions in pain scores, increased likelihood of resolution of sensitivity to pinprick and improvement in size of altered area to brush than those without warm sensitivity resolution. It has also illustrated the value of QST in this area of research. In the future, it may also have merit in the assessment of novel pharmacological interventions for CIBP. In the meantime, the possibility of a link with thermal sensitivity warrants further investigation. At present we are able to show which patients respond best using QST after treatment, but whether findings pre-XRT can be predictive needs evaluation. This will be explored further in the next few chapters.

Chapter 6 CLINICAL CHARACTERISATION OF CIBP

6.1 Introduction

The pilot work described in Chapter 5 indicated that there was utility in the use of QST to characterise the sensory aspects of CIBP and to improve understanding of the underlying mechanisms. It also suggested that QST may have clinical utility as a potential predictor of response to treatment. This needs to be explored in a larger study to allow further investigation of clinical biomarkers. Pain rarely occurs in isolation and is multifaceted, and therefore pain assessment should be multi-dimensional to take this into account. It is also apparent that a comprehensive pain assessment tool is lacking.

The purpose of this prospective observational study was to address these issues. The study aims were:

- To confirm the findings of the pilot work characterising the sensory aspects of CIBP using QST in a larger patient population (Chapter 6).
- To develop a tool to assess the different components of CIBP: cognitive, affective, sensory and functional (Chapter 6)
- To use this technique to evaluate the effects of treatment (XRT) (Chapter 7)
- To establish whether this can be used as a clinical biomarker of response to XRT (Chapter 8).

Subsequently, the hope is that this method of CIBP assessment can be utilised to guide use of chemotherapy, XRT and innovative drug therapies, and may have applications in other chronic pain syndromes.

6.2 Method

6.2.1 Study Population

Patients with CIBP from any primary site, undergoing standard treatment such as palliative XRT, were recruited to the study through the Edinburgh Cancer Centre.

6.2.2 Inclusion Criteria

Subjects were included in the study if they met all of the following criteria:

- Diagnosis of malignant bony metastases, supported by histological or radiological investigations.
- Presence of CIBP.
- Male or female, aged 18 years or over at study entry.
- Fully aware of the current stage of their cancer and its implications for their prognosis and treatment.
- Usual medical team agree to their taking part in the study.
- Written informed consent to participation in the study.
- Ability to complete the various assessments.
- ECOG score of ≤ 2 and a life expectancy which would allow participation for the duration of the study.

6.2.3 Exclusion Criteria

Subjects were excluded from participating in the study if they met any of the following criteria:

- Pathological fracture at index pain site.
- Spinal cord compression.
- Confusion or significant psychiatric illness.
- Unstable or rapidly deteriorating clinical condition.
- Any other medical condition that would confound the objectives of the study.
- Patients who would be adversely affected by study participation, including those unaware of the presence of progressive disease or who would find completion of the study too burdensome.
- Inability to complete the study protocol for any other reason.
- Inability or refusal to provide written consent to inclusion in the study.
- Primary source of pain that does not originate from bony malignancy.

6.2.4 Study Design

The study was granted ethical approval by the Lothian Local Research Ethics Committee for a single site in July 2007. Suitable patients with CIBP were identified on attendance for routine treatment, at the outpatient clinic, on the inpatient wards and by screening the XRT booking forms. Written informed consent was obtained from all patients. Procedures followed were in accordance with the International Committee for Harmonisation (ICH), Good Clinical Practice (GCP) and the Helsinki Declaration. The study was kindly funded and monitored by the Translational Medicine Research Collaboration (TMRC). This Collaboration comprises four of Scotland's leading universities (Edinburgh, Aberdeen, Glasgow and Dundee) working with Wyeth Pharmaceutical Company, Scottish Enterprise and NHS Scotland. Insurance / indemnity were provided through the NHS indemnity scheme or professional indemnity. The project was co-sponsored by NHS Lothian and The University of Edinburgh. Cognitive, affective, sensory and functional assessments were completed at baseline (pre-treatment), 6-8 weeks and 3-4 months after treatment for CIBP. This treatment was part of their planned routine care. Other data recorded on the initial visit included basic demographics, analgesics and all other treatments. All assessments were carried out by one examiner (ACS). Once the research was completed, the participants continued to receive their standard management as appropriate at the Edinburgh Cancer Centre. The ethical, R&D and sponsorship approval letters, patient information sheet, G.P. letter and consent form are included in the Appendix.

6.2.5 Research Tools

The following assessment tools (see Chapter 4) were utilised to characterise the pain syndrome during the study:

- Cognitive & psychological aspects: included the VAS and the following:
    - Short form Brief Pain Inventory
    - Short form McGill Pain Questionnaire
    - Hospital Anxiety and Depression Scale
    - Fear and Avoidance of Pain Scale
    - Pain Catastrophizing Scale.

- Functional impairment: assessed the degree to which a patient's pain may limit their overall walking ability using a GAITRite Electronic Walkway. General function was monitored using an ambulatory physical activity meter (activPAL).
- Sensory aspects: assessed with QST.

All reference to pain was specific to the site of CIBP being treated (or to the worst site of CIBP if more than one area required treatment). Responses after treatment referred only to the pain in the site treated at baseline. As already described, the best parameters of QST to measure have evolved during the course of this research. In this study, pin prick measurement and corresponding VAS were recorded as a measure of mechanical pain sensitivity as opposed to suprathreshold level. MDT and MPT were still measured with von Frey filaments. The area of abnormal sensation with brush was not measured. Temporal summation (wind up) was added to the paradigm, allowing calculation of the wind up ratio. This was calculated as the ratio of the repetitive pin prick stimuli pain rating (VAS of wind up) divided by the single pin prick stimulus VAS score.

6.2.6 Statistical Analysis

Pilot work of sensory changes using QST in 17 patients indicated that the sensory changes were so marked that the proposed sample size of a minimum of 40 new patients (before and after XRT) was adequate to obtain meaningful data. After further ethical approval, the number of patients required for recruitment was increased to 60 during the study, due to the attrition rate in this palliative population.

In the analysis of the baseline data described in this chapter the Minitab® 15 Statistical Software package was used. Descriptive statistics were used for demographic, treatment and disease-related characteristics. Questionnaire, functional assessment results (activPAL and GAITRite) and QST results were described as medians and ranges. The non-parametric Wilcoxon signed rank test was used to compare differences between the CIBP site and control site in QST testing. The Mann-Whitney test was used to compare differences between patients with

CIBP and healthy controls, and between patients with abnormal and normal sensation. Pearson correlation coefficients were used to evaluate associations between pain and the other variables. A p value of less than 0.05 was considered statistically significant. The statistical analysis of the follow-up data is described in subsequent chapters.

6.2.7 Complementary Laboratory Work

In conjunction with the clinical study, funding was allocated to the laboratory part of the translational team. In their work, components of clinical assessment were paralleled by tests in an animal model of CIBP, in which MRMT-1 rat mammary carcinoma cells were injected into the intramedullary canal of the tibia in anaesthetised rats. Assessments were carried out at various time points before and after XRT to the site of CIBP. The sensory aspects were assessed by paw withdrawal to von Frey filaments and thermal stimuli to determine the presence of ipsilaterally limited hyperalgesia and allodynia. Functional impairment was evaluated by weight bearing assessment and paw guarding behaviour in a hotrod test or activity monitor test. These are able to measure the impact of spontaneous pain and movement-induced pain respectively. Lastly, psychological parameters were measured using an elevated T maze test (anxiety) and a tail suppression test (depression). The results of this laboratory work, although vital to the understanding of the mechanisms of CIBP in combination with the clinical study, will not be presented in this thesis as it is not the work of the author.

6.3 Results

6.3.1 Demographics

Between July 2007 and January 2009, 61 patients with CIBP were recruited. One patient deteriorated clinically prior to the first assessment and was withdrawn from the study before completing any study assessments. Therefore, baseline data were available for 60 patients prior to receiving treatment for CIBP. The demographic characteristics are shown in Table 17. The median year the primary diagnosis was made was in 2003 (range 1973-2008) and for bony disease it was 2007 (range

1999-2008). All except one patient had metastatic disease as the cause of their CIBP; one patient had lung cancer causing CIBP as a consequence of locally advanced disease. Most patients (93%) had multiple sites of bony disease. Additional sites of metastases were most commonly liver and lung. Fifty-three patients (88%) were assessed in the outpatient clinic, and seven (12%) were seen during an inpatient admission.

Table 17. Baseline characteristics

		No. of Patients	%
Sex	Male:Female	25:35	42:58
Age (yrs)	Median (range)	63.5 (38-88)	-
ECOG PS	0	12	20
	1	30	50
	2	18	30
Marital Status	Married	32	53
	Partner	5	8
	Single	5	8
	Widowed	8	13
	Divorced	9	15
	Separated	1	2
Employment	Employed	10	17
	Unemployed	0	0
	Homemaker	2	3
	Retired	38	63
	Off due to illness	10	17
Primary Tumour	Breast	31	52
	Prostate	15	25
	Lung	9	15
	Colorectal	2	3
	Renal	1	2
	Myeloma	1	2
	Bladder	1	2
Number of Sites of Bony Disease	None	1	2
	Single	3	5
	Multiple	56	93
Other Metastases	Bone only	35	58
	Extra-osseous	25	42

As can be seen in Table 18, this was a heavily pre-treated population. Two thirds of patients had received previous XRT (either the primary tumour or for metastatic disease). As reflected in the proportion of patients with breast and prostate cancer, current or past hormone use was also fairly common. The most frequent analgesics prescribed for CIBP were weak or strong opioids and NSAIDs. Adjuvants were much less commonly used. All opioid analgesia was converted into a 24 hour morphine equivalent dose using standard conversion ratios (262). Median 24 hour dose at the first assessment was 24mg (mean 69mg, range 0-800mg). Seven patients (11%) had tried either acupuncture or a TENS machine for their index site of CIBP.

Table 18. Treatment

		No. of Patients	%
Prior Cancer Treatment*	Chemotherapy	25	42
	XRT	40	67
	Hormones	34	57
	Radioisotopes	0	0
	Surgery	33	55
	Bisphosphonates	18	30
Current Cancer Treatment*	Chemotherapy	9	15
	XRT	59	98
	Hormones	37	62
	Radioisotopes	2	3
	Surgery	0	0
	Bisphosphonates	28	47
Analgesia*	Simple	20	33
	Weak opioid	28	47
	Strong opioid	27	45
	NSAID	27	45
	Anticonvulsant	8	13
	Antidepressant	3	5
	Lignocaine patch	5	8

*Patients received more than one type of treatment

Primary treatment of CIBP in one patient in the study was strontium. (This patient did not complete a second or third visit.) All the remaining patients had XRT as treatment of their index pain (Table 19). The most common site of CIBP requiring treatment was vertebral disease. Eighty percent of XRT was single fraction, although a quarter of patients had more than one site of CIBP treated at their first visit.

Table 19. Site of CIBP and XRT treatment

		No. of Patients	%
Site of Index Pain (& XRT)	Spine	21	35
	Sacrum/Pelvis	20	33
	Lower limb	3	5
	Sternum/Ribs	11	18
	Shoulder/Humerus	5	9
Dose of XRT (cGy)	800 in 1	48	80
	2000 in 5	8	13
	2000 in 10	2	3
	3000 in 10	1	2
	None	1	2
Number of Sites of XRT at Visit 1	One	44	73
	Two	14	23
	Three	2	3

6.3.2 Cognitive and Affective Assessment

At baseline, all patients completed five questionnaires. The results are shown in Tables 20 to 22. As can be seen from the BPI results, median pain intensity throughout the preceding 24 hours for patients with CIBP varied from a least score of one to a worst score of seven. CIBP also had an influence on functional activities as seen in Figure 13, with highest impact on general activities and normal work.

Table 20. Baseline BPI results (n=60)

BPI	***Median***	***Range***
Worst Pain (/10)	7	1-10
Least Pain (/10)	1	0-5
Average Pain (/10)	4	0-10
Now Pain (/10)	2	0-10
% Pain Relief (Analgesics)	70	1-100
Functional Interference Score (/70)	29	0-64
Total BPI Score (/120)	49	8-96

The results from the MPQ are shown in Table 21. The pain descriptors most commonly chosen for CIBP were "aching" (83% of patients), "gnawing" (63%), "tiring-exhausting" (58%) and "tender" (52%). Twenty-three percent used "hot-burning" as a descriptor and "splitting" was the least frequently used.

Figure 13. BPI functional interference scores

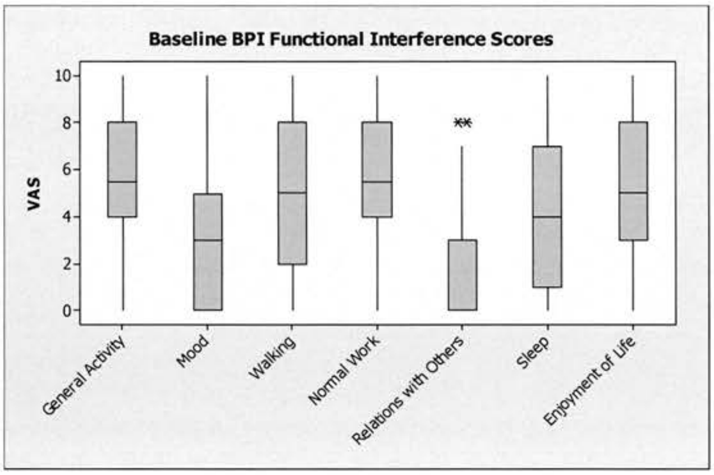


Table 21. Baseline MPQ results (n=60)

MPQ	**Median**	***Range***
Sensory Total (/33)	9	1-26
Affective Total (/12)	2	0-12
Total PRI (/45)	11.5	1-33
Present Pain Intensity (%)	0 No Pain	18
	1 Mild	38
	2 Discomforting	33
	3 Distressing	7
	4 Horrible	3
	5 Excruciating	0

The HADS, FAPS and PCS results are shown in Table 22. Using the HADS subscale, eight patients (13%) had scores indicative of clinical anxiety and eight (13%) indicative of depression. A further six (10%) and 12 (20%) were classified as having "borderline" scores for anxiety and depression respectively. Twenty patients (33%) were classified as having clinically significant emotional distress, as defined by a total HADS score of 15 or above. The most frequent score for all the individual questions in the HADS was either zero or one (out of three), except for the statement "I feel as if I am slowed down" in which 43% of patients answered "nearly all the time", representing a maximum score of three. Only two percent of patients scored it as zero ("not at all"). In the FAPS questionnaire, the statements which had the highest percentage of patients scoring a maximum score of six (i.e. occurring "all the time"), related to avoidance of lifting heavy objects, caution about bending and inability to do normal work. The activities with the lowest impact from CIBP involved social contact with family and friends. Thirty-five percent of patients "strongly agreed" that they "should not do activities which increase my pain" and a further 20% were "unsure". Twenty-eight percent of patients "strongly agreed" that "activities that cause more pain might be harmful" and a further 42% were "unsure" about this. Similar to the HADS questionnaire, the PCS scores were commonly low, but questions relating to rumination and magnification generally scored higher than helplessness.

Table 22. Baseline HADS, FAPS & PCS results (n=60)

		Median	*Range*
HADS	Anxiety (/21)	5	0-17
	Depression (/21)	6	0-14
	Total HADS (/42)	11	1-30
FAPS	Total FAPS (/126)	66	4-120
PCS	Rumination (/16)	3	0-16
	Magnification (/12)	2	0-8
	Helplessness (/24)	2	0-24
	Total PCS (/52)	6.5	0-44

6.3.3 QST Results

There was clear evidence of altered sensory processing due to CIBP. Abnormalities of both mechanical and thermal sensation were seen as outlined in Table 23, with alterations in sensation at the CIBP site compared with control (CO). Allodynia to various QST parameters was also noted. When pain intensity was rated using the VAS, no statistically significant differences were seen between the CIBP and control site secondary to brush (p=0.18) and warm (p=0.13) stimuli. However, significant differences were seen for cool (p=0.036), pin prick (p=0.018) and wind up (p=0.001). In 15 cases, the wind up ratio (WUR) could not be calculated in the CIBP site because the denominator (VAS rating for pin prick stimulus) was zero. In those that could be calculated (n=45), the median wind up ratio was one (range 0-2). Median WUR at the control site was also one (range 0-4) in 38 patients. The difference between the WUR at the CIBP area and control was not significant (p=0.45).

Table 23. Baseline QST results (n=60)

	Brush		*Cool*		*Warm*		*Pin prick*		*Wind up*	
	CIBP	**CO**	**CIBP**	**CO**	**CIBP**	**CO**	**CIBP**	**CO**	**CIBP**	**CO**
Sensation: **Normal**	27 (45%)	60 (100)	10 (17)	60 (100)	14 (23)	60 (100)	18 (30)	60 (100)	24 (40)	60 (100)
Reduced	16 (27%)	0 (0)	23 (38)	0 (0)	13 (22)	0 (0)	13 (22)	0 (0)	11 (18)	0 (0)
Increased	17 (28%)	0 (0)	27 (45)	0 (0)	33 (55)	0 (0)	29 (48)	0 (0)	25 (42)	0 (0)
Painful: **Normal**	0 (0%)	0 (0)	0 (0)	0 (0)	0 (0)	4 (7)	11 (18)	38 (63)	9 (15)	34 (57)
Reduced Sensation	0 (0%)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	6 (10)	0 (0)	6 (10)	0 (0)
Increased Sensation	3 (5%)	0 (0)	6 (10)	0 (0)	8 (13)	0 (0)	28 (47)	0 (0)	25 (42)	0 (0)
VAS:										
Median	0	0	0	0	0	0	2	1	2	1
Range	0-6	0	0-7	0	0-5	0-8	0-9	0-7	0-9	0-7

Differences were also noted between the CIBP and control site in MDT and MPT as measured by von Frey filaments (Table 24). However, when pain secondary to the stimulus was rated using the VAS, the differences between the CIBP and contol site did not reach significance.

Table 24. Baseline von Frey filament results (n=60)

		MDT			*MPT*		
		CIBP	**Control**	**P value**	**CIBP**	**Control**	**P value**
Pressure g/mm2	Median	7.3	7.3	0.83	31.6	57.8	0.015
	Range	1.7-31.6	1.7-31.6		7.3-137	7.3-96.1	
VAS	Median	0	0	0.09	3	3	0.07
	Range	0-4	0-6		0-9	1-9	

6.3.4 Functional Assessment Results

All patients completed an assessment of gait with the GAITRite electronic walkway. Each patient walked along the mat at a "normal" pace between two and four times and the results were amalgamated by the GAITRite system to provide an average set of parameters for gait at the baseline assessment. The results for velocity, cadence and FP are shown in Table 25. These parameters were chosen for analysis as they were felt to be the most relevant clinically in this population. The aim of treatment of patients with CIBP in terms of function is to improve general mobility and ability to carry out activities of daily living. More detailed measures of gait may be more suitable in another setting, for example, after orthopaedic surgery or assessment of orthotics. However, because this is a novel use, there is no evidence to provide guidance or confirmation of the best parameters to measure in CIBP.

Table 25. Baseline GAITRite results (n=60)

	Median	*Range*
Velocity (cm/s)	81.7	20.2-151.4
Cadence (steps/min)	96.8	43.7-128.3
FP Score	84	47-100

FP = Functional Ambulation Performance

For the second part of the functional assessment, patients were given an activity meter prior to undergoing treatment. Data were unavailable for one patient because they declined wearing the meter after completing the rest of the assessment, due to nervousness about how to look after it. In the other 59 patients, the meter was worn for a median duration of 12.4 (range 1-17.2) days. Because most patients were seen for their baseline assessment on the day of their treatment, it meant that the majority of the recording covered the two week period immediately after treatment. However, because it is unlikely that XRT would have a significant analgesic effect in this timescale, this was felt to be representative of a baseline recording. To complete a two week assessment fully prior to treatment would be difficult, as ideally the time between oncology review and treatment is as short as possible.

The activPAL data from the CIBP patients was compared with data from similar recordings in a group of healthy volunteers comprising nine men and four women, with a mean age of 59 (range 47-74) years. Unfortunately, it was not possible to compare energy expenditure between the two groups, due to a difference in calibration and hence calculation of the MET/hour in the samples. Sitting/lying in the healthy volunteers was allocated a MET of one, rather than 1.25 (258). However, all other parameters were examined and as seen from Table 26, the CIBP patients were a statistically significantly frailer, less active population.

Table 26. Baseline activPAL results & comparison with healthy volunteers

		CIBP Patients n=59	Healthy Volunteers n=13	P value
Daily hours sit/lying	Median	19.8	18.1	<0.0001
	Range	16.5-23.8	13.5-20.5	
Daily hours standing	Median	2.9	3.6	0.033
	Range	0.1-5.5	2.3-7.4	
Daily hours stepping	Median	0.9	2.5	<0.0001
	Range	0.02-2.3	1-3	
Daily hours up	Median	4.2	5.7	0.0002
	Range	0.2-7.5	3.3-10.4	
Energy expenditure (MET/hr)	Median	31.9	N/A	N/A
	Range	30.1-35.3		
Daily number of steps	Median	3918	10566	<0.0001
	Range	71-12225	4970-14323	
Daily number of transitions	Median	42	58	0.0001
	Range	14-83	46-107	

6.3.5 Relationships between Pain, Sensation, Mood and Function

The relationship between pain intensity and altered sensation was examined. Patients with abnormal sensitivity to brush, cool, warm, pin prick and wind up had higher baseline worst pain scores (Table 27).

Table 27. Association between baseline worst pain score and QST

QST Parameter	*Abnormal Sensation (↑ or ↓)*		*Normal Sensation*		*P value*
	Number of pts	**Median Worst Pain Score**	***Number of pts***	***Median Worst Pain Score***	
Brush	33	7	27	6	0.032
Cool	50	7	10	5	0.098
Warm	46	7	14	5.5	0.085
Pin prick	42	7	18	6.5	0.053
Wind up	36	7	24	6.5	0.039

To assess the strength of association between the individual items of the BPI at the baseline assessment, Pearson correlation was performed. The results are shown in Table 28. Worst pain score correlated significantly with all the functional interference items, but most strongly with general activity, normal work and enjoyment of life ($p<0.001$). General activity, enjoyment of life and normal work were also highly correlated with other items. The lowest correlations were found between walking and mood, walking and relations with others, and walking and sleep.

Table 28. Pearson correlation between worst pain and functional interference

	Worst pain	General activity	Mood	Walking	Normal work	Relations with others	Sleep	Enjoyment of life
Worst pain	1							
General activity	0.540 *	1						
Mood	0.389 **	0.471 *	1					
Walking	0.389 **	0.457 *	0.088	1				
Normal work	0.498 *	0.685 *	0.371 **	0.509 *	1			
Relations with others	0.291 ***	0.484 *	0.487 *	0.106	0.390 **	1		
Sleep	0.396 **	0.374 **	0.499 *	0.120	0.338 **	0.521 *	1	
Enjoyment of life	0.590 *	0.550 *	0.594 *	0.369 **	0.531 *	0.432 **	0.518 *	1

*$p<0.001$; **$p<0.01$; ***$p<0.05$

Although affective measures in general were perhaps lower than might be expected, there was evidence of an association between CIBP and mood, as well as fear-avoidance and catastrophizing. Table 29 shows the BPI worst pain score and functional interference subscale in relation to the total scores from the other questionnaires. Significant correlations were also found between worst pain score and MPQ sensory ($p<0.001$), MPQ affective ($p<0.001$), HADS anxiety ($p<0.001$), HADS depression ($p<0.001$), PCS rumination ($p<0.001$), PCS helplessness ($p<0.001$) scores, and PCS magnification score ($p<0.01$).

Table 29. Pearson correlation between questionnaires

	Worst pain	*BPI functional interference*	*MPQ PRI total*	*Total HADS score*	*Total FAPS score*	*Total PCS score*
Worst pain	1					
BPI functional interference	0.628*	1				
MPQ PRI total	0.635*	0.562*	1			
Total HADS score	0.610*	0.608*	0.536*	1		
Total FAPS Score	0.473*	0.681*	0.592*	0.531*	1	
Total PCS	0.607*	0.523*	0.545*	0.721*	0.395**	1

*p<0.001; **p<0.01;

The relationship between worst pain score and the objective measures of function was also assessed. Correlations were found between gait and worst pain score with a decrease in all gait measures (velocity (-0.366; p=0.004), cadence (-0.266, p=0.04) and FP (-0.362; p=0.05)). Similarly, correlations were seen between the functional interference BPI score and velocity (-0.347; p=0.007), cadence (-0.339; p=0.008) and FP (-0.344; p=0.007). The activPAL did not show a statistically significant correlation with either worst pain score or the functional interference subscale.

Some affective measures were also found to correlate with function, with a relationship between fear avoidance and both gait and activPAL measures. Pearson correlation demonstrated a significant relationship between FAPS score and velocity (-0.483; p<0.001), cadence (-0.417; p=0.001), FP (-0.490; p<0.001), daily hours up (-0.354; p=0.006), daily energy expenditure (-0.384; p=0.003) and daily number of steps (-0.385; p=0.003). Pain catastrophizing was associated with function when measured with the GAITRite (p<0.02 for velocity, cadence and FP), but not when assessed with the activity meters. Mood, as measured by the HADS questionnaire, was not correlated with either the GAITRite or activPAL measures.

6.4 Discussion

The aims of the research presented in this chapter were to develop a tool to assess the various characteristics of CIBP and to advance the pilot work described in Chapter 5. Each aspect of the assessment process will be discussed individually.

6.4.1 Demographics of Patients with CIBP

In comparison with the patients recruited in the pilot work, the demographic characteristics were very similar in terms of age, gender and primary diagnosis as shown in Table 30. This is unsurprising, as both populations came from the same geographical area and referral source. These figures are largely representative of those undergoing treatment for CIBP in general (120, 162, 273, 274). The site of CIBP being investigated and median 24 hour morphine equivalent analgesic dose were also comparable between the pilot and current research (26mg and 24mg respectively).

Table 30. Comparison of demographics

		Pilot Study (n=45)	*Current Study (n=60)*
Median age (range)		66 (33-83) years	63.5 (38-88) years
Sex (%)	Male:Female	44:56	42:58
Primary diagnosis (%)	Breast	42	52
	Prostate	24	26
	Lung	13	15

6.4.2 Effect of CIBP on Cognition and Mood

As shown in the last chapter, the results confirm the temporal variability of CIBP and the importance of measuring worst pain score, highlighting the problem of breakthrough pain and its impact on quality of life. This has been shown in other studies of CIBP using the BPI (Table 31). Consistently, worst pain score is a few points higher than average pain or pain now.

Table 31. Comparison of median BPI scores for CIBP at baseline assessment

	Pilot Study	***Current Study***	***Hadi(274)***	***Hadi(273)***	***Li (160) Harris(162)***	***Chow (275)***
Number of patients	45	60	52	348	199	909
Worst Pain	8	7	7	8	8	8
Average Pain	5	4	*	*	5	*
Pain Now	4	2	*	*	3.5	*
General activity	5.5	5.5	6	8	8	7
Mood	5	5	5	5	6	5
Walking ability	5	5	6	7	8	7
Normal work	6.5	5.5	7	8	8.5	8
Relations with others	0.5	0	3.5	2	2	3
Sleep	5	4	5	5	5	5
Enjoyment of life	6	5	6	8	8	7

* Information not provided

Using the short form MPQ to look at the words used to describe CIBP confirmed that bone pain is commonly aching and gnawing in character, but nearly half of all patients also classified their pain as sharp, shooting and stabbing, which is highly likely to represent either evoked breakthrough pain or perhaps a neuropathic element to the pain. This neuropathic component was also suggested in a quarter of patients by the use of the words hot and burning. It is well recognised that bony metastases can cause symptoms from nerve root compression, for example. It is also known from animal models that the pathophysiology of CIBP is unique, and while it has neuropathic and inflammatory-like components, it differs from neuropathic and inflammatory pain (39). However, used in conjunction with QST findings, the MPQ may provide useful information to enhance our understanding of CIBP. In addition, the 6-point present pain intensity (PPI) scale of the MPQ showed that current pain was either mild or discomforting which was in agreement with the median "pain now" score of two as measured with the BPI. This verbal PPI tool has been shown to be easily understood in a previous study of prostate cancer patients with CIBP (90). Although in that study the long version of the MPQ was used and was felt to be too difficult.

However, the value of a "pain now" score is limited as worst pain score seems to correlate more strongly with interference with function. In addition, in the current study it was interesting to see that using the NRS in the BPI to assess "pain now" with each number shown compared with the MPQ VAS with descriptors only at each end (Figure 14) did not always give equal scores despite instruction from the examiner. Although the median difference between the two scores was zero, ten patients rated their current pain one point or more (i.e. $\geq$1cm on VAS) higher on the BPI NRS than the MPQ VAS. Conversely 16 patients rated their pain $\geq$ one point less with the BPI NRS than the MPQ VAS. This is shown in Figure 15. As discussed in Chapter 4, both methods are well validated, although the VAS is felt to be more difficult and may be affected by patient age and education (138). Thus, the differences seen in this study may reflect ease of use, population demographic or perhaps individual issues with dexterity and visuospatial awareness. It is less likely to have been due to actual differences in the current pain score as both questions were answered within a short period of time. Although the VAS and NRS are felt to be equivalent and have been shown to be correlated significantly in terms of pain intensity (276), a number of other studies of both acute and chronic pain have shown differences between these two methods within individuals (164, 169). In both of these studies, there was a tendency towards higher pain intensity ratings with the NRS than the VAS.

Figure 14. "Pain now" as assessed by the BPI and MPQ

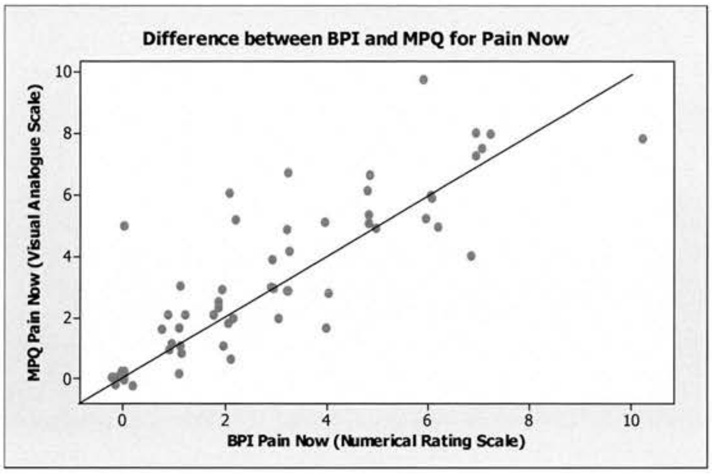
A) BPI NRS

Please rate your pain by circling the one number that tells how much pain you have right now.										
0 No Pain	1	2	3	4	5	6	7	8	9	10 Pain as bad as you can imagine

B) MPQ VAS

No Pain	______________________	Worst Possible Pain

Figure 15. Difference between pain intensity ratings with VAS and NRS



The HADS questionnaire was well accepted by patients and revealed similar scores for anxiety as found in previous studies in cancer patients. In the current study, mean anxiety subscore was 5.5. Moorey et al. (185) used the HADS in 568 cancer patients and found a mean score of 5.4 and Smith et al. (187) had a mean score of 6.05 in 1474 cancer patients. (No median scores were available for comparison.) Using a score of eight or more to suggest pathology (borderline or caseness), the proportions of patients said to have anxiety was 23%, 27% and 33% in the three studies respectively. Looking at the depression subscale in a similar manner revealed that depression scored higher than anxiety in our study compared with the other two. Mean depression score in the current study was 6.1 compared with 3.02 as measured by Moorey et al. (185) and 4.38 by Smith et al. (187). Percentages with possible depression were 33%, 8.7% and 19.8% respectively. One explanation for the difference in prevalence of depression may be the stage of cancer. Only 10.4% had metastatic disease in one study and in the other study patients had various stages of disease. This theory is strengthened further by Lloyd-Williams et al. who used the HADS to assess 100 palliative patients with metastatic cancer with a prognosis of six months or less (189). In this setting, 53% of patients scored eight or more on the anxiety scale and 63% scored at or above this level for depression. The authors also noted that the statement "I feel as if I am slowed down" was scored as three in 74% of patients. The high scoring for this question was also seen in the current work, in which 43% of patients answered "nearly all the time". Lloyd-Williams et al.

confirmed the high sensitivity of this item, but its very low specificity reflecting its poor discriminatory power for depression in palliative patients (189).

An alternative method of evaluating the HADS uses a total cutoff score of 15 or more to represent clinically significant emotional distress (184). Walker et al. found that this gave a sensitivity of 0.87 and specificity of 0.85 and a positive predictive value of 0.35 for major depressive disorder in mixed cancer outpatients (191). A subsequent survey to estimate the prevalence of distress in outpatient cancer patients found that 674 out of 3071 (22%) had scores of 15 or more (190). In our study, patients with significant psychiatric history were excluded, but despite this 33% were classified as having significant emotional distress. Again, this higher percentage may be related to the stage and extent of disease, as in the work by Strong et al., two thirds of patients attending the clinics were disease-free (190).

There is little in the literature with which to compare the results of the FAPS questionnaire as fear avoidance has mainly been assessed in conditions such as chronic musculoskeletal pain. Models have been proposed to describe how psychological factors influence chronic pain to look at the relationship between pain-related fear and disability (201). The theory is that fear responses may be linked with greater pain behaviour through psychophysiological mechanisms or through an association with avoidance (203). In this way, higher pain expectation may result in reduced movement during activity. This may be particularly relevant for patients with CIBP with movement-evoked pain. Fifty-seven percent of patients agreed (35% strongly) that they should avoid activities which increased pain and 42% were fearful that activities that cause more pain might be harmful (28% agreeing strongly). Another issue highlighted when assessing patients with CIBP using the FAPS, was that a large proportion of patients were "unsure" about what may or may not be harmful in terms of activity, often in fairly simple aspects of daily life, due to lack of appropriate information from health care professionals. Increasing patient education may potentially help subsequent fear avoidance behaviour.

Catastrophizing refers to a negative response style characterised by a tendency to ruminate on aspects of the pain experience, to exaggerate the threat value of pain and to adopt a helpless orientation to pain (206). The PCS has been used to study coping in breast cancer patients (210), but otherwise most of the literature relates to non-cancer pain, and so there is little with which to draw comparisons. However, it seems that the level of catastrophizing in this population of patients with CIBP was surprisingly low. The mean total PCS score was 11.3 (median of 6.5), whereas in other studies of chronic benign pain, mean scores of 20.85 (277), 25.3 (278), and 30.7 (279) were seen with the PCS. Sullivan et al. found mean scores ranging from 20.7 to 26.2 in three groups of patients with pain of non-malignant neuropathic origin (209). Osman et al. compared the PCS score between 215 pain-free adults with 60 patients with pain (280). Similarly to the scores in the studies above, the mean score in the group with pain was 22.25 compared with 13.87 in healthy adults, which is higher than in our patients with CIBP. It is not immediately clear why this is, although the questionnaire was not designed for patients with active cancer. One study has suggested that scores of 28 or more in the PCS are clinically significant (281). This was the case in 13% of CIBP patients.

Overall, despite being a frailer population with significant pain, all 60 patients were able to complete the five questionnaires without any major difficulty providing a comprehensive characterisation of the cognitive and affective aspects of CIBP. In addition, correlation between the questionnaires was strong.

6.4.3 Effect of CIBP on Sensory Processing

Analysing CIBP using QST as a method of sensory assessment strengthens and adds to what is already understood about the underlying pathophysiological mechanisms. As in the pilot study, the findings suggest abnormalities in sensory processing with demonstration of both peripheral and central sensitisation. In the current study, a smaller proportion had dynamic mechanical allodynia to brush testing than the pilot work, but this is still indicative of dysfunction of Aβ fibres. In addition, a high proportion of patients in the current study had abnormal sensitivity to thermal stimuli, indicating disruption of smaller Aδ and C fibres. Again, the proportions of patients with pain to these stimuli were lower in this study than in the pilot. Large differences between the CIBP and control site were seen, in terms of altered sensation to stimulus (i.e. increased or reduced sensitivity), and statistically significant differences were shown for pain severity with certain stimuli. Thus, perhaps both the quality of the sensation and the intensity are relevant when testing sensory processing in patients with CIBP.

In this study, wind up was also assessed by delivering a train of pin prick stimuli of the same force within a small area at a rate of 1/second. This was a refinement of the paradigm in the pilot in which wind up was not used. Sixty percent of patients were shown to have altered response to wind up in the CIBP site compared with control. The majority of these showed a heightened sensitivity, although 18% of all patients had reduced sensation with this stimulus. Previous studies using QST, have suggested that the wind up ratio (WUR) should be calculated (211, 218). This has the potential to provide useful information, but in this study a large portion of WURs could not be calculated. This was the case in 37 of 120 wind up tests (37%) done at the first assessment. This is significantly higher than the figure of 1.1% quoted by Rolke et al. in healthy volunteers (218). Therefore, a higher proportion of patients rated intensity due to mechanical pain as zero both in the CIBP site and the control site. Whether this is a reflection of the tool being used or whether there is a difference in the way those with chronic severe pain rate intensity compared with pain free individuals is not clear. A pin prick may appear relatively painless in comparison with the pain of bony metastases. However, this does not explain the fact that no significant difference was observed between the WUR in the CIBP and control sites.

However, the main reason for assessing wind up was to address the presence of central sensitisation. The presence of wind up in CIBP points to activation of the NMDA receptor and therefore NMDA antagonists may be a potential therapeutic option in cases with clinical evidence of central sensitisation. In the pilot study, although wind up was not assessed the area of abnormal sensation was measured and it was seen that the size of the receptive field lessened after treatment, providing further evidence of the plasticity in the dorsal horn. Unfortunately, the size of the sensory abnormality was not measured in the current study for a number of reasons. Patients were generally seen for their first assessment in the hour prior to XRT, and there was concern by the examiner that adding pen marks to the treatment field may cause inconvenience during treatment planning. Secondly, to be able to provide accurate measurements requires time. Patients in this study were undergoing a significantly larger number of assessments during each visit to incorporate evaluation of the affective and functional aspects of CIBP compared with the last study. Therefore, measurement of the area of sensory abnormality was omitted to limit additional burden to the patient.

The paradigm used in this research was well understood and accepted by patients and had the advantage of being performed by only one examiner throughout the whole study. However, it could be criticised for being too simple in comparison with the protocol by Rolke et al. (218). In their work, a full sensory profile takes an hour to complete, but this is not practical in our setting for a variety of reasons as discussed in Chapter 4. Patients with advanced disease with significant pain would be unlikely to tolerate such a detailed QST protocol. Many patients with CIBP find it hard to sit comfortably for long periods of time. Three quarters of patients agreed that they "tend not to stay in one position too long as it increases my pain" as measured with the FAPS questionnaire. Fatigue is also likely to be an issue in frailer patients and for QST to be accurate requires alertness and concentration. In addition, time constraints are a reality. The aim of this work was to find a tool that may be of use in the clinical setting and a shorter paradigm is more useable. It is also for this reason that the tools used in this study were more basic handheld instruments. For example, computer based systems allow accurate measurement over a large range of thermal thresholds and the current study only measured response to one temperature for either warm or cool. However, this was understandable for patients and they tended to be very clear in their response, whether it was the same, reduced or increased in comparison with the control site. This method of response to stimuli was found to be of benefit in a study by Andersen et al., in which sensibility to touch, temperature and pin prick were assessed in patients after a stroke to evaluate the presence of central post-stroke pain (282). As with the current study, Andersen et al. used the contralateral area as the control. The use of such relative reference data with right and left comparisons in CIBP patients was felt to be appropriate as it is said to be more sensitive than absolute reference data for picking up positive and negative sensory signs (218). However, there is a slight concern using this method in patients with CIBP as commonly they have multiple sites of disease, and the "normal" side may also have underlying pathology, even if painless. In addition, in patients with CIBP in the spine in the midline, an alternative level was used as the control as a side to side comparison was not possible.

6.4.4 Effect of CIBP on Function

Using the GAITRite electronic walkway was a very simple method for patients with which to measure function. The only disadvantage was the time taken to set it up beforehand due to the lack of a dedicated area. Ideally, the walkway should be permanently laid out in a room designed for the purpose. However, once it was set up it allowed gait analysis within a very short time frame. In this part of the functional assessment, no data were collected from a healthy population to use as a direct comparison. Although the GAITRite system can alert the user to values out with a normal range when a walk is done, this only applies to a small age range. Therefore elderly patients, as in this study, could not be compared directly with the in-built data. Thus, it is useful to look at results from other studies which use the GAITRite system. The comparisons are shown in Table 32. The mean values are reported, as median values were not discussed in the studies.

Table 32. Differences in gait between healthy subjects and CIBP patients

	Current study	***Bilney(239)***	***Van Uden(253)***	***Menz(252)***	
Number of Subjects	60	25	21	30	31
Population	CIBP patients	Healthy adults	Healthy adults	Healthy adults	
Age Range	38-88	21-71	19-59	22-40	76-87
Velocity (cm/sec) (self-selected pace)	81.9	146	142.49	144	117
Cadence (Steps/min) (self-selected pace)	95.5	114.74	Not given	111.48	107.89

There are no studies with which to compare these GAITRite parameters in cancer patients. However, it can be seen that compared with healthy adults, including an older group of subjects, patients with CIBP walked much more slowly and had lower cadence. The data from the activity meters also suggested that patients with CIBP are a less active, frailer group. Significant differences were seen in comparison with healthy controls. Physical activity has previously been shown to be impaired in cancer patients using the activPAL meters. In this group of patients with advanced upper gastrointestinal cancer undergoing chemotherapy, median time spent upright was 3.8 hours per day (258). The equivalent in CIBP patients was 4.2 hours per day. Patient acceptability of the activity meters seemed to be high. Using a transparent film Tegederm™ dressing rather than the adhesive pads provided proved popular, as the breathable film enabled showering. A common quote was that patients "forgot it was there". Of a total of 127 activPAL assessments over the whole study period (including follow up assessments), a mild reaction to the dressing was seen twice. Both cases resolved without requiring additional intervention and only one required discontinuation of use of the meter.

6.4.5 Relationships between Pain, Sensation, Mood and Function

Associations between the multi-dimensional components of CIBP were seen. Demonstration that those patients with abnormal sensitivity to QST stimuli had generally higher worst pain scores suggests a relationship between sensory nerve dysfunction and intensity of CIBP.

There was a relationship between CIBP and mood. Those with the highest worst pain scores had higher HADS scores (Figure 16). Individuals with CIBP with higher worst pain scores also appeared to have higher pain catastrophizing scores (Figure 17). A similar pattern was seen with fear avoidance. Increasing awareness of these cognitive and affective problems in patients with CIBP may allow appropriate management and improvement in quality of life. It is less clear, however, whether a causal relationship exists between these factors. In a systematic review by the author, this question was examined in relation to cancer pain and depression (142). The initial literature search revealed 892 articles, of which 41 were independently reviewed and 14 were eligible for inclusion. The mean prevalence of both depression and pain was 36.5% (range 22.1-49%). In nine of the studies a statistically significant association was demonstrated between pain and depression. Pain intensity positively correlated with depression ($p<0.05$). It was also shown that the longer the duration of pain, the higher the risk of depression. However, the evidence available was not sufficient to support an interdependent relationship due to lack of appropriately designed studies. In a similar manner, attributing causality in the CIBP patients in the current study was not possible, but it is well known that psychiatric disorder is under-recognised and under-treated in cancer patients impacting on quality of life, with reduced compliance with treatment and poorer outcomes (283, 284). Perhaps screening for depression in such populations should be integrated into the care pathway (285). It will be important to see whether or not treatment of CIBP impacts on the levels of mood disturbance. This will be discussed in subsequent chapters.

Figure 16. Relationship between worst pain score and mood at baseline

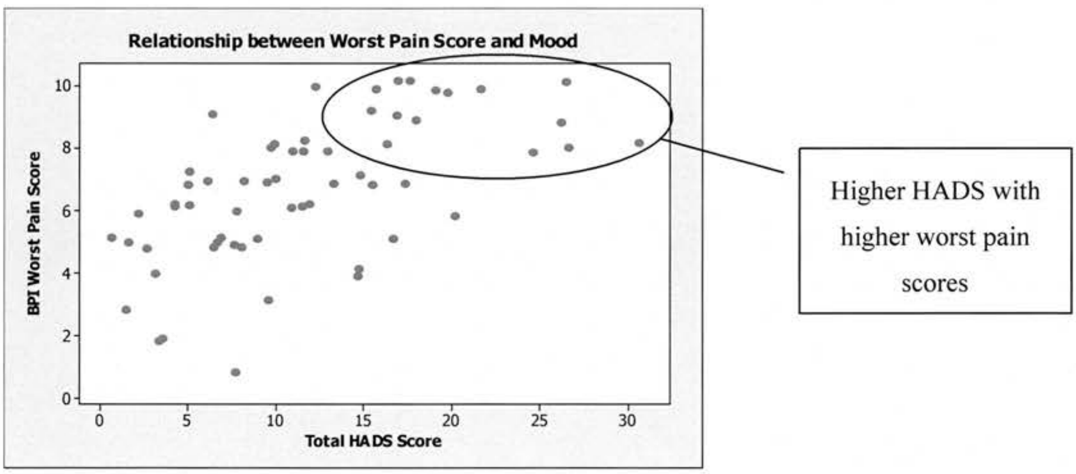
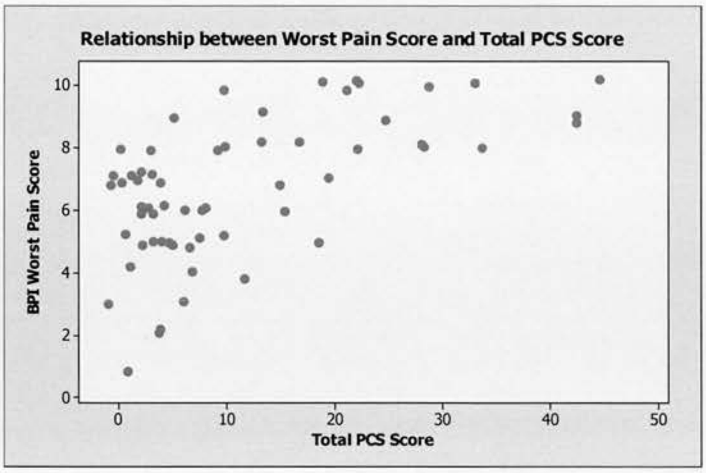
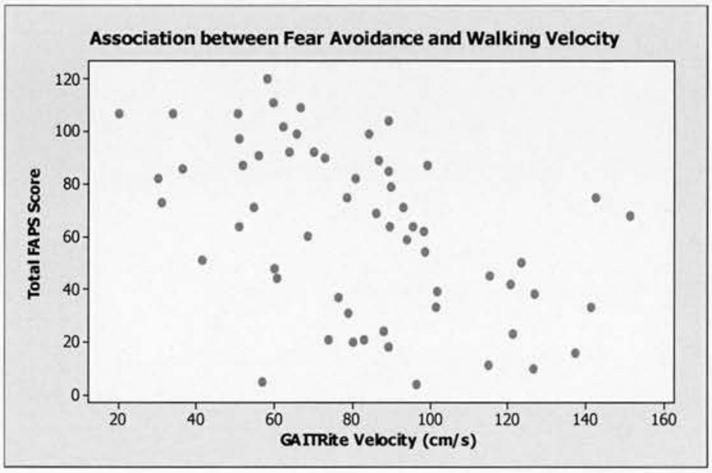


Figure 17. Relationship between worst pain score and catastrophizing at baseline



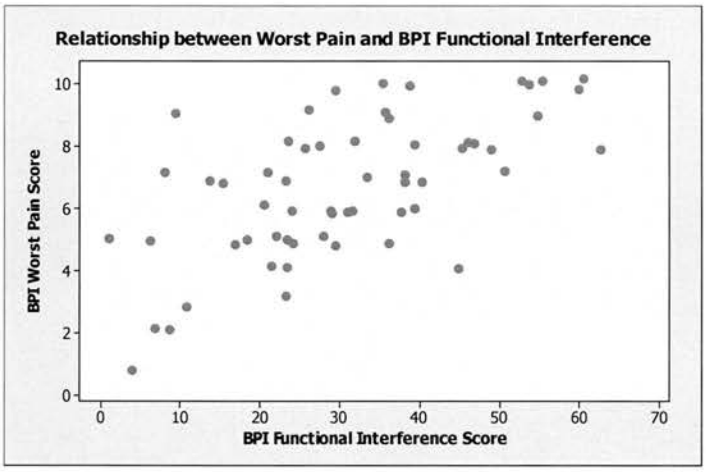
Whether fear avoidance behaviour relates to more functional disability in cancer patients was examined by looking at the relationship between the questionnaire results and the GAITRite and activPAL data. Significant correlations were found between fear avoidance and both of these objective measures of function. For example, as the FAPS score increased, walking velocity tended to decrease (Figure 18).

Figure 18. Relationship between fear avoidance and function



However, although catastrophizing was associated with gait, when function was measured with the activity meters there was no relationship. Perhaps the measurement of gait is more sensitive for those patients in whom the severity of incident pain may be related to catastrophizing, whereas the activity meters may be confounded by other factors such as fatigue. This is only speculative, but may also be a reason why worst pain score was associated with gait, but no correlation was seen between worst pain score and the activity meter results. However, interference of CIBP with function was clearly seen using the BPI (Figure 19). Generally, as the worst pain score increased, total functional interference score increased. Worst pain score was also highly correlated with the individual functional interference items. This is in agreement with other studies which have shown the high correlations with general activity, normal work and enjoyment of life as well (162, 273-275).

Figure 19. Relationship between worst pain score and functional interference



6.5 Conclusion

CIBP is common and may impact on vital aspects of a patient's life such as cognition, mood and activity. It remains a considerable therapeutic challenge because it is a complex pain syndrome. Despite this, CIBP has been a neglected area of clinical research. There is a clear need for increased understanding of the mechanisms of bone pain in order that novel, effective pain killers can be developed and the management of this challenging problem can be improved. By linking symptoms with mechanisms the aim is to develop treatment that can target the most distressing symptoms. Objective and measurable evidence is vital and currently a comprehensive standardised assessment tool is lacking. The purpose of this research was to develop such a tool, which could be used to measure the cognitive, affective, sensory and functional components of CIBP. This aimed to provide a thorough method of characterising the multi-dimensional aspects of pain due to bony metastases and, in addition, examination of the sensory changes which can be related to pain processing.

In this study, using a clearly defined combination of assessments, patients with bony metastases were able to have their pain characterised. This appeared to be practical and acceptable to the population studied. All were able to complete the baseline assessment. It demonstrated that it is vital not only to measure pain intensity at the time of the assessment, but also worst pain to reflect the issue of difficult to control breakthrough pain. The temporal fluctuations are important to record to increase the chances of optimal pain control. It was also seen that CIBP is associated with psychological aspects of pain such as anxiety, depression, fear avoidance and catastrophizing. Correlations were seen between worst pain score and the functional interference scores of the BPI, but in addition worst pain score correlated with aspects of gait, an objective measure of function. Use of the GAITRite walkway and the activPAL were novel in this setting of CIBP, but they demonstrated a large reduction in activity and performance compared with healthy subjects. This reduced function was associated with fear avoidance and catastrophizing. QST allowed further examination of the sensory aspects of CIBP. It confirmed preliminary data showing the dysfunction of both large and small sensory fibres, and the presence of central sensitisation. It adds to the understanding of the plasticity of pain pathways in bone pain, along with the work done in animal models of CIBP.

In summary, the baseline assessment has allowed successful characterisation of the cognitive, affective, sensory and functional aspects of CIBP. In the next chapter, the results of using this method to evaluate the effects of treatment for CIBP are presented.

Chapter 7 CIBP: RESPONSE TO PALLIATIVE RADIOTHERAPY

7.1 Introduction

In the last chapter a number of tools were used in combination to provide an assessment of CIBP which encompassed all the various aspects of the pain experience. Linking symptoms with signs using QST helped increase current understanding of the underlying mechanisms. It was also seen that pain severity was associated with psychological factors such as mood, fear avoidance and catastrophizing, which in turn were related to function. Objective measures of activity revealed that this was a group with significantly impaired function compared with healthy adults. Patients with CIBP have significant morbidity associated with their pain. One of the possible advantages of a comprehensive assessment is the potential for intervention of these associated issues. In this respect, involvement of a multi-disciplinary approach to care is likely to be of benefit. Another advantage of a multi-factorial assessment is that relationships can be explored between the different components and the changes can be examined before and after an intervention. It is difficult to determine causality, but it is of interest to see whether the cognitive, affective, sensory and functional aspects of CIBP alter with treatment of the pain. The utility of the instruments to be able to do this is described in this chapter.

7.2 Method

The study criteria and assessment tools used in this part of the work are as previously described. Patients who had completed an initial baseline assessment prior to treatment for CIBP were invited to undergo a second and third assessment. These were completed at 6-8 weeks and 3-4 months after XRT. The assessment was identical to that done at the first visit. The results of the assessment at 6-8 weeks are discussed below. The first part of this analysis looked at all patients completing two assessments as one group. These patients were then compared to those who dropped out of the study.

Subsequently, a more detailed analysis was carried out to examine the characteristics of those patients who gained a clinically significant analgesic response to XRT (Chapter 8). The final visit at 3-4 months is discussed in Chapter 9.

7.2.1 Statistical Analysis

In the analysis of the follow up data described in this chapter, the Minitab® 15 Statistical Software package was used. Descriptive statistics were used to summarise the demographic results before and after XRT. As with the baseline data, questionnaire, functional assessment results and QST results were described as medians and ranges. The Wilcoxon signed rank test was used to compare differences between the CIBP site and control site in QST testing and to analyse the changes between baseline and follow-up in all the other parameters. The Mann-Whitney test was used to compare the characteristics of patients completing two assessments and those who dropped out of the study after one assessment. Univariate and multivariate analyses were performed to look for independent predictors of those patients unable to complete two assessments. A p value of <0.05 indicated statistical significance.

7.3 Results

Effect of XRT on All Patients at 6-8 Weeks

Out of the 60 patients who completed a baseline assessment prior to treatment for CIBP, 42 (70%) were able to complete a second assessment. All 42 patients had received XRT as the primary treatment of their pain.

7.3.1 Demographics

Of the 42 patients who completed two assessments, 16 (38%) were male and 26 (62%) female, with a median age of 65.5 years (range 38-88 years). Marital status, employment status, primary tumour type, site of index pain and fractionation schedule in these patients was very similar to the whole population seen at baseline. Proportionally slightly more prostate cancer and slightly less lung cancer patients were able to complete a follow up assessment. Performance status improved after XRT with proportionally more patients PS zero and less PS two (Table 33).

Table 33. Demographics (n=42)

		Visit 1 (Pre XRT)	*Visit 2 (Post XRT)*
ECOG PS	0	24	31
(%)	1	55	55
	2	21	7
	3	0	7

Anti-neoplastic and analgesic treatments before and after XRT and are shown in Table 34. A higher percentage of patients were undergoing chemotherapy at this follow up visit than at the baseline assessment, and 14% required further XRT for CIBP. For one patient this was to be re-treatment to the same site of CIBP (which was given after the follow up assessment); the remaining patients were receiving XRT to new sites of CIBP. After XRT, proportionally more patients were on a strong opioid, and less on a weak opioid. However, there was no statistically significant difference between the 24 hour morphine equivalent dose after treatment.

Table 34. Treatment at visits 1 & 2 (n=42)

		Visit 1 (Pre XRT)		*Visit 2 (Post XRT)*	
		No.	**%**	**No.**	**%**
Current Cancer Treatment* (%)	Chemotherapy	5	12	12	29
	XRT	42	100	6	14
	Hormones	28	67	26	62
	Radioisotopes	1	2	0	0
	Surgery	0	0	1	2
	Bisphosphonates	19	45	22	52
Analgesia* (%)	Simple	11	26	13	31
	Weak opioid	22	52	12	29
	Strong opioid	15	36	21	50
	NSAID	19	45	14	33
	Anticonvulsant	5	12	7	17
	Antidepressant	1	2	1	2
	Lignocaine	1	2	0	0
24hr Morphine Dose (mg)	Median	24		22 (p=0.085)	
	Range	0-272		0-260	

*Patients received more than one type of treatment

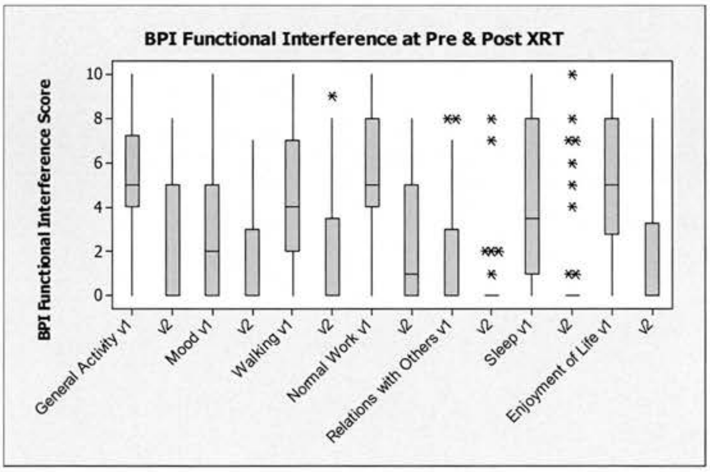
7.3.2 Cognitive and Affective Results

All 42 patients completed the questionnaires with no missing data. This was achieved due to the supervision of the examiner. Overall, pain improved after XRT with statistically significant reductions in all questions of the BPI as shown in Table 35. The change in the individual functional interference items is shown in Figure 20.

Table 35. BPI results at visits 1 & 2 (n=42)

BPI		*Visit 1 (Pre XRT)*	*Visit 2 (Post XRT)*	*P value*
Worst Pain	Median	7	3	<0.001
	Range	1-10	0-10	
Least Pain	Median	1	0	0.004
	Range	0-5	0-6	
Average Pain	Median	4	1	<0.001
	Range	1-10	0-7	
Now Pain	Median	2.5	0	<0.001
	Range	0-10	0-7	
Functional Interference Score	Median	27.5	4.5	<0.001
	Range	4-64	0-51	
Total BPI Score	Median	48	11	<0.001
	Range	8-98	0-72	

Figure 20. Difference in BPI functional interference before and after XRT



A similar effect was seen with the MPQ after XRT. Sensory score improved from a median (range) of nine (1-26) to three (0-19) ($p<0.001$), affective score from two (0-11) to zero (0-9) ($p=0.008$) and total PRI score fell from 11 (1-33) to three (0-22) ($p<0.001$). There was also a large change seen in present pain using the PPI of the MPQ as shown in Table 36.

Table 36. MPQ results at visits 1 & 2 (n=42)

MPQ		*Visit 1 (Pre XRT)*		*Visit 2 (Post XRT)*	
		No.	**%**	**No.**	**%**
PPI (%)	0 No Pain	7	17	28	67
	1 Mild	17	40	8	19
	2 Discomforting	15	36	5	12
	3 Distressing	2	5	0	0
	4 Horrible	1	2	1	2
	5 Excruciating	0	0	0	0

Although HADS scores were generally low before and after treatment, mood significantly improved with XRT. Median anxiety, depression and total scores changed from 4.5 (range 0-17) to three (0-18) ($p=0.012$), five (0-14) to four (0-15) ($p=0.046$), and nine (1-30) to seven (1-30) ($p=0.009$) respectively. In addition, the percentage of patients classified with clinically significant emotional distress (total HADS score of $\geq$15) fell from 31% (13/42) pre XRT to 17% (7/42) post XRT. A marked improvement was seen in levels of fear avoidance with a significant reduction in median total FAPS score from 61 (range 4-111) to 24.5 (0-111) post XRT ($p<0.001$). Pain catastrophizing also significantly improved (Table 37).

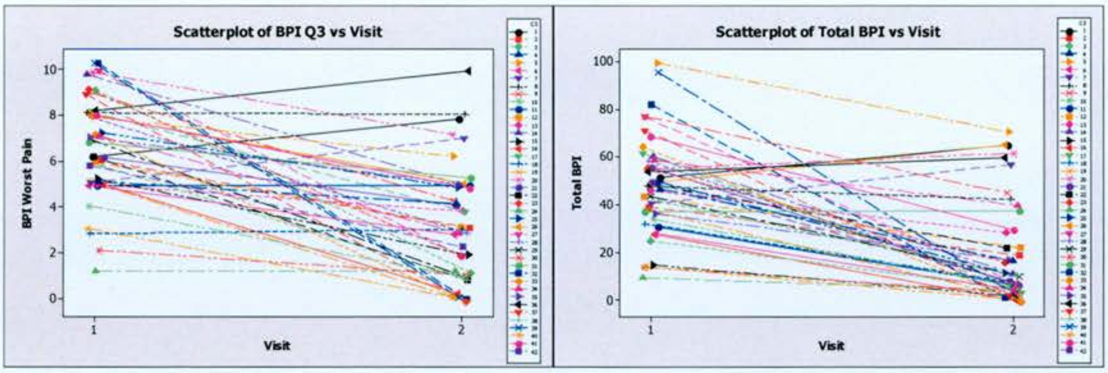
Table 37. PCS results at visits 1 & 2 (n=42)

		Visit 1 (Pre XRT)	*Visit 2 (Post XRT)*	*P value*
Rumination	Median	3	0	0.003
	Range	0-16	0-16	
Magnification	Median	2	1	0.025
	Range	0-8	0-12	
Helplessness	Median	2	1	0.011
	Range	0-20	0-13	
Total PCS	Median	7	2	0.003
	Range	0-42	0-38	

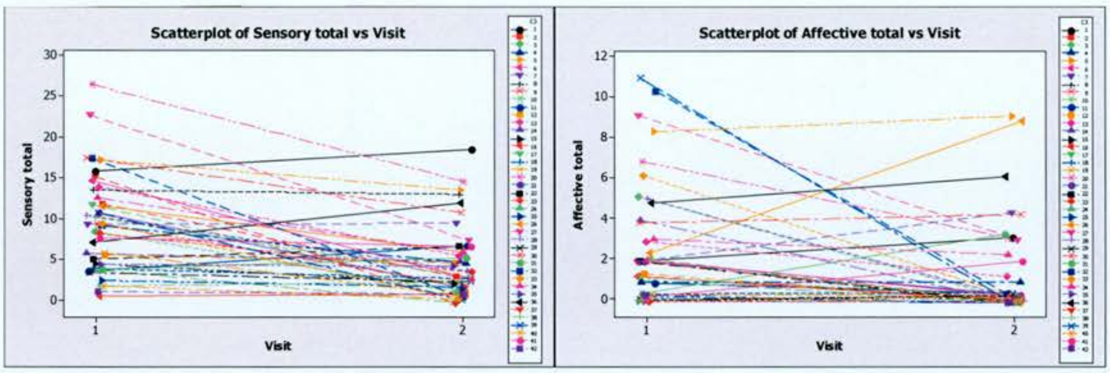
Using scatterplots to show the trends among individuals confirms the general improvement in questionnaires after treatment, and clearly shows those patients who have not responded (Figure 21).

Figure 21. Questionnaire scores at baseline (visit 1) and 6-8 weeks (visit 2)

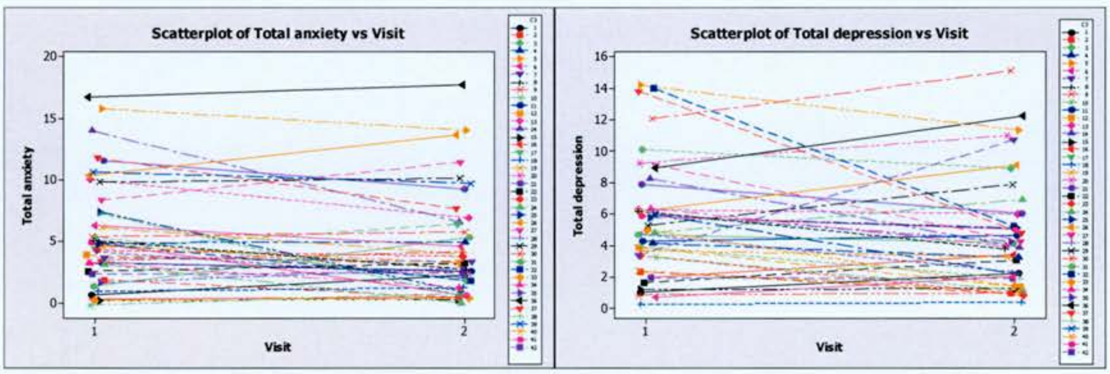
A) Worst & Total BPI scores



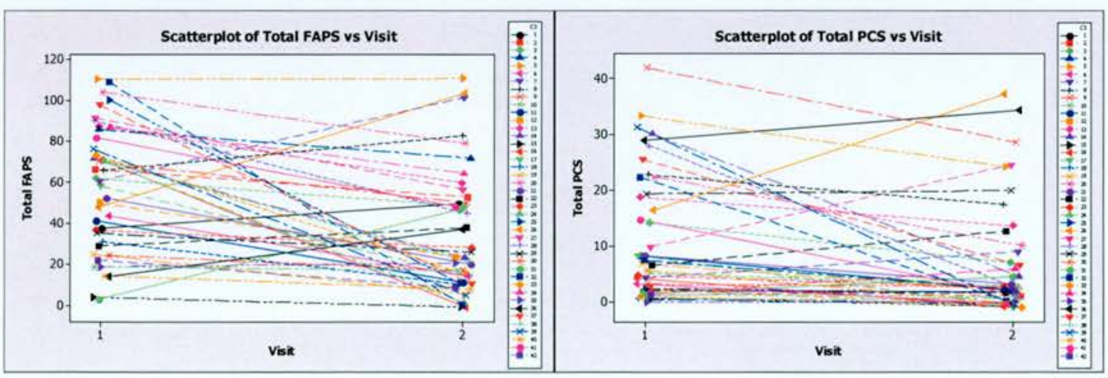
B) Sensory & Affective MPQ scores



C) Anxiety & Depression HADS scores



D) Total FAPS & PCS scores



7.3.3 QST Results

There were marked changes in QST in response to XRT in both mechanical and thermal parameters (Table 38). Abnormalities in response to dynamic mechanical stimulus resolved in 12 patients with 21/42 (50%) having normal brush sensation pre XRT and 30/42 (71%) post XRT. (Three patients had normal sensation pre XRT which became abnormal after XRT). Two patients had dynamic mechanical allodynia which resolved after treatment. There was no significant change in MDT and MPT in response to XRT (Table 39). Numbers of patients with normal response to noxious pain (pin prick) and wind up increased from 12 (29%) to 23 (55%) and 17 (40%) to 19 (45%) respectively after XRT. There was a significant reduction in median VAS for noxious stimulation (two to zero, $p=0.009$), but not for wind up. Thermal abnormalities were affected by XRT, with abnormal cool sensation resolving in 14 patients (8/42 normal pre XRT and 17/42 post XRT, with five patients with sensation changing from normal to abnormal post XRT). Abnormal warm resolved in 12 patients (12/42 normal pre XRT and 19/42 post XRT; sensation in five patients changed from normal to abnormal post XRT).

Table 38. Change in sensation before and after XRT at CIBP site

Sensation Pre XRT	*Sensation Post XRT*	*Brush*	*Cool*	*Warm*	*Pin prick*	*Wind Up*
Normal	Normal	18 (43%)	3 (7%)	7 (17%)	6 (14%)	10 (24%)
Abnormal	Abnormal	9 (21%)	20 (47%)	18 (43%)	13 (31%)	16 (38%)
Abnormal	Normal	12 (29%)	14 (33%)	12 (28%)	17 (40%)	9 (21%)
Normal	Abnormal	3 (7%)	5 (12%)	5 (12%)	6 (14%)	7 (16%)

Table 39. MDT & MPT before and after XRT

		Visit 1 (Pre XRT)		*Visit 2 (Post XRT)*	
		CIBP	**Control**	**CIBP**	**Control**
MDT(g/mm2)	Median	7.3	7.3	7.3	7.3
	Range	1.7-31.6	1.7-25	3.3-39.1	3.3-25
MDT VAS	Median	0	0	0	0
	Range	0-4	0-2	0-1	0-2
MPT (g/mm2)	Median	31.6	57.8*	39.1	57.8
	Range	7.3-96.1	17.5-96.1	7.3-137.3	7.3-137.3
MPT VAS	Median	3	3	3	2
	Range	1-9	1-9	0-9	0-8

* Statistically significant difference between CIBP & control site ($p=0.015$)

The sensory change in relation to analgesic response will be discussed in Chapter 8.

7.3.4 Functional Assessment Results

Out of the 42 patients who attended for a second visit, 40 completed an assessment of gait. Although the velocity, cadence and FP improved after XRT, the differences were small and not statistically significant (Table 40). Patients wore the activPAL for a median of 12.6 days for the baseline assessment and 11.8 days for the follow up assessment. Forty-one patients wore the activity meter a second time. No statistically significant differences were seen before and after XRT with the activity meter (Table 41).

Table 40. GAITRite parameters before and after XRT (n=40)

		Visit 1 (Pre XRT)	*Visit 2 (Post XRT)*	*P value*
Velocity	Median	86.4	88.7	0.79
(cm/s)	Range	36.4-151.4	31.6-150.7	
Cadence	Median	99.9	101.5	0.69
(steps/min)	Range	52.2-128.3	66.1-126.3	
FP Score	Median	85.5	86.5	0.96
	Range	56-100	53-100	

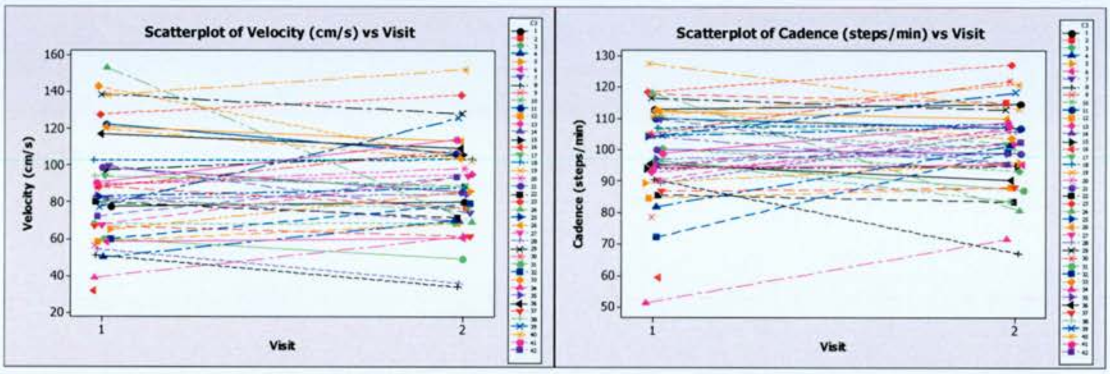
Table 41. activPAL results before and after XRT (n=41)

		Visit 1 (Pre XRT)	*Visit 2 (Post XRT)*	*P value*
Daily hours sit/lying	Median	19.7	20	0.91
	Range	16.5-23.8	14.7-23.8	
Daily hours standing	Median	3.3	2.8	0.73
	Range	0.1-5.5	0.1-7.5	
Daily hours stepping	Median	0.9	1	0.51
	Range	0.03-2.3	0-3.7	
Daily hours up	Median	4.3	4	1.00
	Range	0.2-7.5	0.2-9.3	
Energy expenditure (MET/hr)	Median	32.1	32.2	0.89
	Range	30.2-35.3	30.1-35.9	
Daily number of steps	Median	4223	4319	0.87
	Range	92-12225	136-13623	
Daily number of transitions	Median	44	44	0.68
	Range	14-83	7-73	

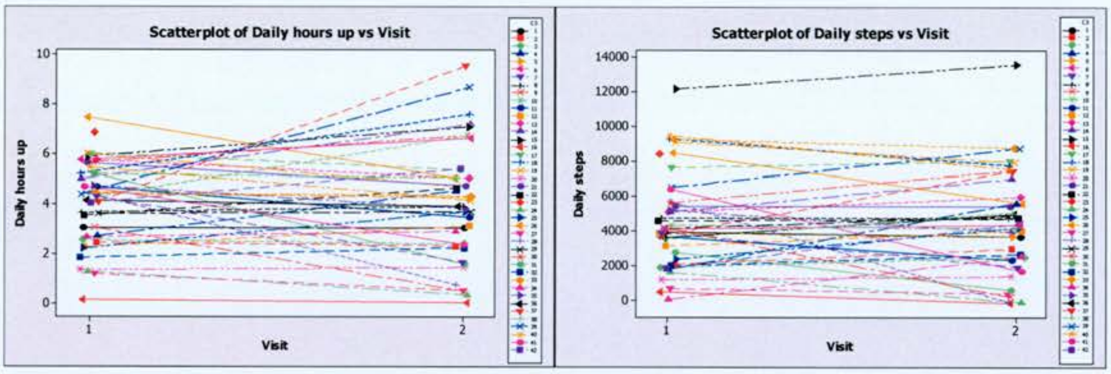
As with the questionnaire results, the functional assessment results were plotted before and after XRT to show the change in individuals (Figure 22). For most of these parameters, the differences were small; hence most lines were almost horizontal. However, a number of individuals had larger changes after treatment, and looking in detail at these patients may help to understand why no significant functional differences were seen.

Figure 22. Functional results at baseline (visit 1) and 6-8 weeks (visit 2)

A) GAITRite Velocity & Cadence



B) activPAL Daily Hours Upright & Number of Steps



Comparison between Patients Completing a Second Assessment and Dropouts

Out of the 60 patients who completed a baseline assessment prior to XRT, 18 (30%) were unable to attend for a second assessment 6-8 weeks after XRT. Reasons for dropping out of the study after the first assessment are shown in Table 42. Of the five patients who died, one was secondary to a pulmonary embolism and four were due to rapid disease progression. A further five patients deteriorated clinically due to the underlying cancer.

Table 42. Reason for withdrawal from study after baseline assessment

Reason for Withdrawal	***Number of Patients***
Death	5
Too unwell (disease progression)	5
Too unwell (other cause)	4
Psychological reason	3
Failed to attend for appointments	1

The baseline results were examined to see if there were any major differences between the 42 patients who were able to complete a follow up visit at 6-8 weeks and the 18 patients that were unable to attend. The demographics of the two groups are shown in Table 43. Those who withdrew were generally of lower performance status and more were seen as inpatients suggesting they were a frailer group. They also showed a trend towards a higher opioid dose (median of 65mg versus 24mg), although this was not statistically significant (p=0.08). Lung patients were less likely to complete two assessments. A slightly higher proportion of women were seen in the patients completing two assessments. Age, marital status, employment, site of CIBP and treatment schedule was similar between the two groups.

Table 43. Demographic results

		Completed 2 visits (n=42)		***Withdrawn (n=18)***	
		Number	%	Number	%
Sex	Male	16	38	9	50
	Female	26	62	9	50
Age (yrs)	Median	65.5		58	
	Range	38-88		41-81	
ECOG PS	0	10	24	2	11
	1	23	55	7	39
	2	9	21	9	50
Place of Assessment	Outpatient	40	95	13	72
	Inpatient	2	5	5	28
Primary Tumour	Breast	22	52	9	50
	Prostate	12	29	3	17
	Lung	5	12	4	22
	Colorectal	1	2	1	6
	Renal	1	2	0	0
	Myeloma	0	0	1	6
	Bladder	1	2	0	0
Other Metastases	Bone only	23	55	12	67
	Extra sites	19	45	6	33

The questionnaire results were compared between those completing two assessments and those withdrawn. No statistically significant differences were seen for the BPI, MPQ and PCS. Pre-treatment median worst pain score was seven in each group. The functional interference score was higher in the dropouts (median of 36.5 vs 27.5), but this did not reach significance. No difference was seen for the total HADS score, although the depression subscale was significantly higher in the dropouts (median score nine vs five, $p=0.04$). There was also a difference in baseline score for the FAPS questionnaire with fear avoidance higher in the patients who withdrew (median score 86 vs 61, $p=0.03$). There were no striking differences between the QST parameters between the two groups.

Difference in function between those completing two visits and those who withdrew was the final aspect of the assessment to be compared. Median velocity, cadence and FP were worse in those who dropped out, but the differences were not significant. However, for all parameters of the activity meter assessment, apart from the daily number of transitions, statistically significant differences were seen between the median results of the two groups (Table 44). This reflects what was seen with performance status. Those unable to return 6-8 weeks after XRT for a second assessment of their CIBP were a physically frailer group from the outset.

Table 44. activPAL results for patients completing two assessment and dropouts

	Completed 2 visits (n=42)	*Withdrawn (n=17)*	*P value*
Daily hours sit/lying	19.7	22.2	0.0082
Daily hours standing	3.3	1.5	0.0141
Daily hours stepping	0.9	0.3	0.0037
Daily hours up	4.3	1.8	0.0082
% time up	26.9	11.2	0.0082
Energy expenditure (MET/hr)	32.1	30.7	0.0019
Daily number of steps	4223	1094	0.0025
Daily number of transitions	44	36	0.056

Univariate and multivariate analyses were performed subsequently to assess whether any of the variables at the baseline visit were independent predictors of those patients unable to complete the study (i.e. the dropouts). In the univariate analysis, performance status ($p=0.032$), HADS depression ($p=0.040$) and total FAPS ($p=0.036$) were predictive. In the gait assessment, cadence ($p=0.041$) was predictive, but velocity ($p=0.057$) and FP ($p=0.051$) did not quite reach significance. However, the strongest predictors of dropout in the univariate analysis were seen with the activPAL activity meter data: daily hours sitting/lying ($p=0.007$), daily hours standing ($p=0.013$), daily hours stepping ($p=0.009$), daily hours upright ($p=0.007$), energy expenditure ($p=0.004$) and daily number of steps ($p=0.007$). In the multivariate analysis, energy expenditure ($p=0.002$) and age ($p=0.022$) were independent predictors, with younger patients more likely to withdraw (although age was not quite significant in the univariate results).

7.4 Discussion

Overall, CIBP improved after XRT. In conjunction with this, improvements were seen with psychological factors such as anxiety, depression, fear avoidance and catastrophizing. Fewer patients were emotionally distressed. Changes were also seen in the sensory aspects of CIBP using QST. In a proportion of patients, abnormal sensitivity to stimuli resolved after XRT. Using the GAITRite walkway and the activity meters as measures of function did not demonstrate any changes after treatment.

This chapter looked at response in the various aspects of CIBP in all patients as one group. This does not examine what differences are seen in those patients with a clinically significant analgesic response to XRT in comparison with non-responders. This will be addressed in the following chapter. Prior to this, various issues regarding the use of these tools to assess response to treatment are discussed.

7.4.1 Effect of XRT on the Cognitive and Affective Component of CIBP

As seen in the last chapter, the BPI has been used frequently to assess CIBP prior to treatment. It has also been shown to be of benefit in demonstrating response to XRT, both in this study and the literature. Hadi et al. showed statistically significant reductions in worst pain score and the functional interference items after XRT for

CIBP (273). Worst pain score improved from median of eight at baseline to four at the eight week follow up. Similar findings were seen in a smaller study by the same author (274). A comparable response was seen by Li et al. (160) and Harris et al. (162). Worst, average and current pain, as well as all the functional interference scores, improved after XRT. At eight weeks post XRT, median worst pain score decreased from eight to four, average pain from five to two and current pain from three to one (160, 162). These findings are very similar to the current study. Also like our study, large improvements in the functional interference items, such general activity, walking ability and normal work, were seen. In a study by Wu et al., mean worst pain score improved from 5.2 to 2.5 after XRT for CIBP in 109 patients (120). As with the other studies, a significant reduction in functional interference was seen in all seven items. In addition, the change in worst pain score after XRT correlated with the change in overall interference score.

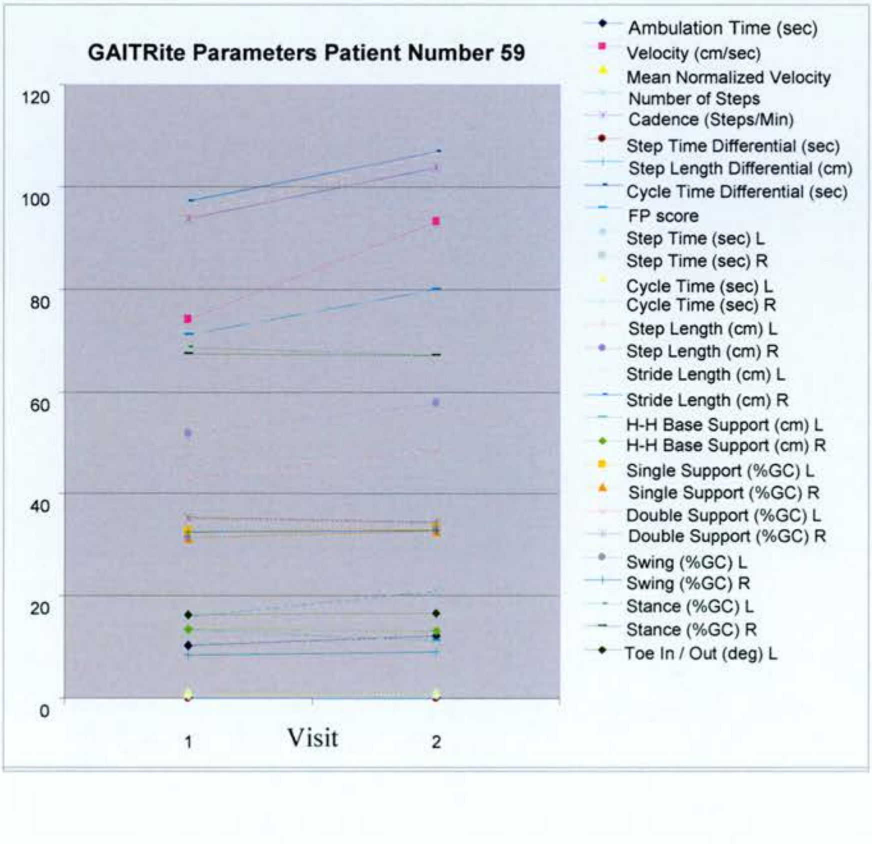
Despite these consistent findings with the BPI, one particular issue was notable when patients were completing the questionnaire. In patients with a single site of CIBP and with no pain from another aetiology, it was fairly straightforward to attribute how much pain was affecting function. However, in those patients with more than one site of pain potentially impacting on activity, trying to separate the relative contribution of the pain at the index site was difficult. For example, if a patient gets partial pain relief at one site of CIBP after XRT (e.g. lumbar spine) and their walking is better as a consequence, then the functional interference score for that item should theoretically be less. However, if that patient has a new site of pain (e.g. hip) which now also interferes with walking, functional interference from pain is worse again. If this new hip pain was included in the interference score rating then this would not provide a true reflection of the effect of XRT at the original site. To try to minimise this problem, when patients completed the BPI at follow up they were asked to respond only in reference to their original site of XRT. This was easier for some patients than others, and was a similar issue when answering other questionnaires, such as the FAPS and PCS. This particular problem was discussed and addressed in the same way in another study (162). A similar problem with measurement of pain with the BPI was highlighted in a study by Stenseth et al. (286). The purpose of the work was to investigate whether the functional interference items were influenced by factors other than pain. Adult cancer patients completed two versions of the BPI. One was an original version which asked to what degree pain interfered with certain functions and the other was a revised version which asked how the functional items were affected in general. In the 48 patients who completed both questionnaires, the scores were similar (except for mood interference which was higher in the modified BPI). The authors concluded that the BPI functional interference items were a global interference measure, rather than specifically related to pain. This relates to the issue discussed above, which questions the ability of patients to report the influence of pain on function without bias from decreased function caused by other factors. Ability to be able to answer these questionnaires accurately is also likely to depend on factors such as cognitive function, educational ability and prior experience. However, in the study by Stenseth et al., the majority of the patients included did not suffer from severe pain and had a generally high level of function (286). Therefore, although the authors raise a valid issue, the observations cannot be generalised to patients with more severe cancer pain, such as CIBP.

The effects of XRT on the cognitive and affective aspects of CIBP will be discussed further in the next chapter.

7.4.2 Effect of XRT on Function

One option to help determine the effect of pain on function is to use objective measures of function rather than subjective responses in a questionnaire. This was one of the aims of the current study with the use of the GAITRite walkway and the activPAL activity meters. In the last chapter these tools were useful to demonstrate the differences between patients with CIBP and healthy volunteers, and they may have some utility in helping determine fitness to participate in research (see below). However, in this chapter no statistically significant difference in the objective measures of function was found after XRT for CIBP, which may be due to a number of reasons. It may be that XRT for CIBP improves pain, but that this does not extend to an improvement in function. This will be explored further in the next chapter when patients are categorised as responders or non-responders and the differences in the various aspects of CIBP are examined in the two groups. An alternative explanation is that functional improvements do occur after XRT, but are too small to be measured with these instruments. This could be explored in a study with much larger numbers of subjects. However, the most likely problem when trying to measure function due to pain is that there are multiple confounding factors. Frequently, patients have concurrent illness, pre-existing co-morbidities, other cancer-related symptoms (such as fatigue or visceral pain) or treatment-related toxicities which may impact on function and mask any changes that result from XRT. It is uncommon for patients to have one site of CIBP as their only symptom with no other coexisting issues. However, in one such "uncomplicated" patient, the potential value of the GAITRite system can be seen (Figures 23 and 24). Figure 23 shows all the parameters measured by the walkway and the changes that occur between visit one (pre XRT) and visit two (post XRT) for this individual, who had no other problems except for a single site of CIBP. Little change is seen in the parameters at the bottom half of the figure.

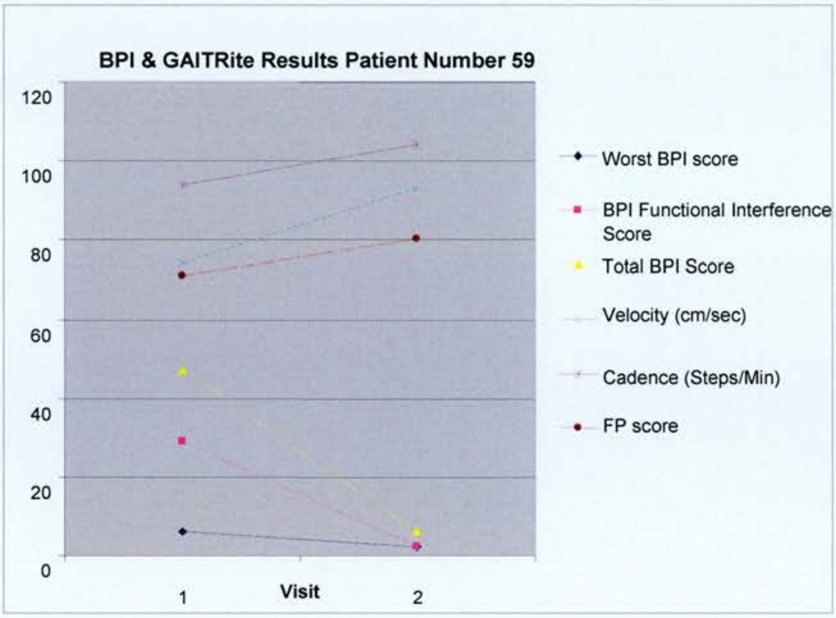
Figure 23. Example of GAITRite results before and after XRT



These more detailed aspects of gait were not felt to be of value in this setting as discussed in the last chapter.

It can be seen from Figure 24 that this patient had an excellent response to XRT with an improvement in worst pain score from six to two, with a large reduction in both functional interference and total BPI scores. In conjunction with this, his gait improved in terms of velocity, cadence and FP score. If all patients were straightforward such as this case, then the GAITRite and activity meters may have been of more benefit in measuring function, but in a large proportion of the population other factors may have impacted on function. This may be an issue in other objective measures of function.

Figure 24. Example of BPI and gait measurements before and after XRT



7.4.3 Effect of XRT on the Sensory Component of CIBP

Research in non-malignant disease has shown the value of QST in assessing changes in somatosensory perception before and after treatment. For example, Kosek and Ordeberg demonstrated the reversal of abnormal sensory findings following successful joint replacement for osteoarthritis (271). So far, we have shown that QST is a useful tool with which to examine the sensory aspects and underlying mechanisms of CIBP. Therefore, it was hoped that its use after XRT would be of value in clarifying its analgesic mechanisms in CIBP. Despite the fact that XRT is the gold standard treatment for CIBP, the mechanism through which XRT decreases pain is not well understood. However, a number of theories are available (24). If patients experience pain relief quickly, within 48 hours of XRT, it may be due to a cytotoxic effect on normal bone cells, resulting in inhibition of the release of chemical mediators of inflammation (268). Conversely, if relief is not seen for weeks, then killing or lysis of tumour cells is involved (268). This time interval correlates well with the beginning of recalcification. However, although treatment of CIBP with multiple fractions of XRT results in significantly more remineralisation than a single fraction of XRT, no significant difference in pain relief is seen (287).

To improve understanding of the mechanisms of XRT for pain, animal models have been used. Reduction of bone pain via a direct effect on tumour cells has been examined by Goblirsch et al. (288). In this research, the effect of a 20 Gy dose of XRT on a mouse model of CIBP was explored. The findings indicated that XRT reduced bone pain and supported decreased cancer burden and decreased osteolysis as the mechanisms. In a separate paper in 2005, the same authors looked at the influence of single localised doses of 10, 20 or 30 Gy to femoral sarcomas in mice (289). Dramatic reduction in pain behaviour and osteolysis were seen with the two higher doses. They also examined the effect of giving XRT prior to tumour injection. This had no effect on tumour growth and pain behaviour and so the authors concluded that the action of XRT is via direct tumour effects.

Using animal models, other authors have suggested that XRT-induced analgesia is related to specific mechanisms other than tumour regression. Seong et al. injected hepatocellular carcinoma cells into the periosteal membrane of the hind foot dorsum in mice (290). A single dose of 25 Gy to the tumour-bearing area was administered 15 days after tumour transplantation. Behavioural responses were measured and included assessment of limb withdrawal to graded mechanical, heat and cold stimuli using von Frey filaments, acetone and halogen lamp. The authors showed that on day 14 there was obvious erosion and destruction of metatarsal bone. From day seven, pain was detected with a statistically significant difference between the tumour and control group for limb withdrawal to mechanical and cold stimulus. No difference was noted with heat stimulus. After XRT, analgesia was evident at three and seven days after treatment. Mechanical pain threshold increased and withdrawal frequency to cold stimulus reduced after XRT. Immunohistochemical analysis of spinal cord was performed seven days after XRT. Expression of SP, c-Fos and CGRP in the spinal cord were examined. After XRT, expression of CGRP decreased compared with untreated animals. SP and c-Fos expression were comparable in both groups. The authors concluded that XRT attenuated the level of pain by altering pain-related signals in the spinal cord, thus mediating the anti-inflammatory effects, rather than occurring via cancer cell eradication. This team then investigated alteration of pain-related signals after XRT by proteomic analysis (260). The same hepatocellular CIBP mouse model was utilised and gel electrophoresis, mass spectrometry and Western blotting were carried out. Twelve proteins were found to have changed more than five-fold secondary to tumour formation, but then reversed after XRT. The proteins involved included secretagogin, syntenin, P2X purinoreceptor 6 and Ca^{2+}/calmodulin-dependent protein kinase I. These are felt to be involved in various pain signalling pathways. The fact that analgesia was observed as early as three days after XRT when no tumour regression was visible, suggested that XRT-induced analgesia is mediated by a mechanism other than cell death in the early phase after treatment.

Rather than using high dose XRT (20 Gy), Vit et al. investigated whether a single low dose of XRT (6 Gy) would produce analgesia (291). Mice were injected with sarcoma cells into the medullary cavity of both humeri. As well as assessing pain behaviour, they assessed changes in markers of inflammation and neural mediators of pain in the spinal cord. After tumour implantation, a decline was seen in pain-related behaviour as measured by the rota-rod and grip force. In the irradiated animals performance improved, whereas it continued to deteriorate in those not treated. XRT was also shown to have an equivalent analgesic effect as the combination of morphine and ketorolac, a non-selective COX inhibitor. By measuring forelimb weight and volume the authors showed that low dose XRT did not affect the growth rate of the tumour 18 days after implantation, suggesting that the differences in performance were not due to tumour size. Therefore, the authors felt that the analgesic effect of XRT was not due to reduction in tumour burden. They also concluded that the mechanism was not secondary to an effect on osteoclasts. This is because although an increase in osteoclast activity was seen after tumour inoculation in both irradiated and non-irradiated models, no difference was seen between the two. Changes were noted in two pro-inflammatory cytokines (monocyte chemoattractant protein (MCP-1) and TNF-α) which increased following XRT. Therefore, reduction in cytokines was not felt to be contributory to the analgesic effect. Lastly, the authors showed that XRT reduced the tumour-induced inflammatory response in the spinal cord. There was a decrease in glial activity (astrocytes and microglial cells) as well as mediators of pain such as dynorphin, COX-2 and chemotactic cytokine receptor (CCR2). Thus, part of the analgesic effect was felt to be due to altered nociceptive processing in the central nervous system.

These animal models examining the mechanism by which XRT works are not consistent in their theories, but there is a suggestion that the sensitisation which occurs secondary to CIBP may be reversible. This was mirrored in the QST findings which demonstrated the normalisation of abnormal sensitivity to specific stimuli in a proportion of patients. It is possible that reduction in dynorphin seen in these models may equate to the reduction of hyperalgesia as measured by QST in humans. However, as with the other tools used to assess pain in this setting, it will be vital to assess whether those patients who did not respond to XRT had different sensory findings after XRT than those who had an analgesic response to treatment.

7.4.4 Patient Attrition

Difficultly with patient attrition in studies of CIBP similar to ours has been shown by a number of authors. For example, in one study 167 of 348 patients (48%) were unable to provide a follow up assessment at the eight week point (273). The main reasons given for lack of follow up were progression of disease and death. Because of attrition, Hadi et al. was able to follow up only 28 of 52 patients (54%) at eight weeks (274). Li et al. (160) and Harris et al. (162) found that 49% (98 patients out of

199) could not be reached for follow up two months after XRT for CIBP. The main reasons were death and hospitalisation. By three months, only 40% of patients seen at baseline were well enough to take part. This is one of the reasons given by the authors for using two months as the optimal time to measure response in this setting. In agreement with our work, the proportion of breast and prostate cancer patients able to carry on with the study was higher than those with lung cancer two months after XRT (160, 162). This most likely simply reflects the poorer prognosis of patients with lung malignancy.

It is well established that identification, recruitment, enrolment, and retention of patients with advanced malignancy in clinical trials is difficult (292-294). It seems that the dropout rate of 30% by eight weeks in our study was fairly modest in comparison to the studies of CIBP described above. The usual way to try to minimise withdrawal is to exclude patients with very low performance status or those with a limited life expectancy. This relies on clinical judgement and medical staff are notoriously inaccurate at estimating both of these (295-297). In addition, some studies may inherently want to recruit frail patients at the end of life if that is the particular focus of the research. However, in most work the aim is to allow as many subjects as possible to complete the study. It would therefore be useful to be able to predict which patients are unlikely to manage to complete a trial, so long as this does not bias the population recruited and the study objectives. In the current work, those patients who completed two assessments were compared with those who did not manage to complete. The latter group had worse performance status at the baseline assessment, but the most noticeable difference between the two groups was measured using the activity meter. Patients who dropped out were much less active, spending less than half as many hours upright and walking only a quarter of the amount of steps per day than those remaining in the study. Energy expenditure was independently predictive. Perhaps a measure of function such as this could have utility in helping decide who might be suitable for study inclusion or fitness to receive a specific treatment.

7.5 Conclusion

The aim of the work in this chapter was to use the method of CIBP assessment developed in Chapter 6 to examine the cognitive, affective, sensory and functional components of CIBP after XRT. Although patient attrition was significant, those who were able to attend the follow up visit were able to complete the assessment without complication. Overall, pain significantly improved with XRT with statistically significant reductions in worst, least, and average pain scores and functional interference as measured by the BPI. In addition, mood, fear avoidance and catastrophizing significantly improved after XRT, with fewer patients classified as being emotionally distressed. No statistically significant differences in objective measures of function were seen after XRT. This may be a true reflection of function after treatment, but alternatively it may have been secondary to the specific tools used, numbers in the study or the impact of confounding factors. However, marked sensory changes were seen in response to XRT. Abnormal responses to a variety of stimuli resolved with treatment, although in a smaller number of patients a change in the opposite direction was seen. As with the other components of CIBP, it will be vital to see whether the changes seen after XRT parallel the analgesic response. This will be examined in Chapter 8.

In summary, using this combination of assessments after XRT for CIBP, a comprehensive picture of the effect of treatment on the various components of pain was possible. This has shown that XRT impacts on multiple aspects of the pain experience. The assessment also has shown potential utility in helping to decide which patients may be suitable candidates for inclusion in clinical research. Those patients who dropped out prior to follow up were significantly frailer as measured with activity meters and performance status, with higher levels of depression and fear avoidance behaviour.

Chapter 8 CLINICAL BIOMARKER DEVELOPMENT

8.1 Introduction

The paradigm of analgesia with a gold standard treatment is key to clinical biomarker development in the area of pain. It has now been shown with the study so far that it is feasible to assess patients with CIBP before and after XRT to determine the baseline characteristics of their pain and the response to treatment in a comprehensive manner. To address all the aspects of the pain experience, the cognitive, affective, sensory and functional components of CIBP were measured with a combination of tools. In the last chapter, it was seen that pain improved with XRT. Associated with this improvement, changes in sensation were demonstrated and psychological benefits were noted in terms of anxiety, depression, fear avoidance and catastrophizing. No significant differences were seen in function (using the GAITRite walkway and activity meters). However, the results so far have reflected the changes after XRT overall in *all* patients. Although XRT is the gold standard treatment for CIBP, it is well established that up to half of patients will not get adequate pain relief (7). The next step, therefore, is to examine patients with an analgesic response to treatment and to compare whether any differences exist between these responders and non-responders. In this way, it should be possible to establish whether the cognitive, affective, sensory and functional aspects of CIBP change after XRT depending on response.

Currently, there are no known clinical predictors of response to XRT for CIBP. By being able to establish in advance who is likely to get an analgesic benefit, would be advantageous for health care resources, clinicians and most importantly the patients. This would allow provision of more individualised care and prevent unnecessary treatment in a frail population with limited life expectancy. As can be seen from the last chapter, a number of patients died within two months of XRT and may not have had a survival long enough to gain benefit from treatment. Having a simple clinical biomarker of response to XRT would have significant clinical, as well as research, utility. The results of the analysis to identify potential predictors of response to XRT for pain control are presented.

8.2 Method

The study criteria and tools used in this part of the work are as previously described. All patients completing a baseline assessment prior to XRT and a follow up assessment 6-8 weeks later were considered eligible for the analysis of response to treatment and investigation of biomarkers.

8.2.1 Statistical Analysis

Patients were categorised as responders (R) or non-responders (NR) according to a predetermined change in *worst* BPI score after XRT. Responders included those with either a complete or partial response. A complete response was defined as a reduction in worst pain score to zero at the irradiated site 6-8 weeks after treatment. A partial response was defined as a reduction in worst pain score of $\geq$ 30% at the irradiated site. Non-responders included those with no response, < 30% improvement in worst pain score, or pain progression. In the preliminary study described in Chapter 5, change in *total* BPI score was used to define response to XRT. This was refined in the current work, as worst pain score was felt to be more clinically relevant in patients with CIBP (for the reasons outlined in Chapter 4). Two months was the optimal time to measure response after XRT for two reasons; maximum pain relief may take more than four weeks to achieve and attrition poses a major problem when response is measured at a later date (160). Analgesic requirements, although recorded, were not included in the definition of response. Although this has been suggested in criteria as an endpoint (115), opinion is still conflicting and it is not felt universally to be a primary endpoint in view of potential interference by numerous other factors (155). In addition, this study did not aim to examine the efficacy of XRT per se, which would require different methodology. Instead this was exploratory work to examine assessment tools and potential predictors of response.

In the analysis described in this chapter the Minitab® 15 Statistical Software package was used. Descriptive statistics were used to summarise the demographic results before and after XRT in responders and non-responders. The Wilcoxon signed rank test was used to compare differences between QST parameters at the CIBP and control site, and also to compare the differences in all other measures before and after XRT. The Mann Whitney test was used to compare differences between responders and non-responders, and to compare patients with abnormal and normal sensation. Regression analysis was used to identify any independent predictors of analgesic response to treatment. A p value of <0.05 indicated statistical significance.

8.3 Results

The 42 patients who had an assessment before and after XRT were divided into responders and non-responders as described. Of these evaluable 42 patients, twenty-nine patients (69%) were classified as responders and 13 (31%) as non-responders. Seven patients (17%) had a complete response to XRT. On an intention-to-treat basis, this equates to a response rate of 48% (29/60).

8.3.1 Demographics

There were some differences in the basic demographics between the two groups (Table 45) with proportionally more men and patients in a relationship in the responders. Differences were also noted in terms of primary tumour type, presence of non-osseous metastases and prior anti-neoplastic treatments. There was no difference between the two groups for site of CIBP and the fractionation schedule. Twenty-one percent of responders and 38% of non-responders were receiving XRT to more than one site of bone pain. Performance status and current treatment in responders and non-responders before and after XRT is shown in Table 46. In responders, performance status improved, fewer patients required additional chemotherapy (14% vs 23%) or additional analgesics (such as NSAIDS and anticonvulsants), and more were on hormonal treatment compared with non-responders. No significant differences were seen between the two groups for morphine requirement before and after XRT.

Table 45. Demographics of responders (R) and non-responders (NR)

		R (n=29)		NR (n=13)	
		Number	**%**	**Number**	**%**
Sex	Male	13	45	3	23
	Female	16	55	10	77
Age (yrs)	Median (Range)	65 (38-88)		66 (49-81)	
Marital Status	Married/Partner	20	69	6	46
	Single/Widowed/ Divorced/Separated	9	30	7	54
Employment	Employed	3	10	4	31
	Unemployed	0	0	0	0
	Homemaker	0	0	1	8
	Retired	22	76	8	62
	Off due to illness	4	14	0	0
Primary Tumour	Breast	14	48	8	62
	Prostate	11	38	1	8
	Lung	2	7	3	23
	Colorectal	1	3	0	0
	Renal	1	3	0	0
	Myeloma	0	0	0	0
	Bladder	0	0	1	8
Site of XRT	Spine	10	34	2	16
	Sacrum/ pelvis	12	41	5	38
	Lower limb	0	0	1	8
	Sternum/ ribs	6	20	3	23
	Shoulder/ Humerus	1	3	2	15
Other Metastases	Bone only	18	62	5	38
	Extra sites	11	38	8	62
Prior Treatment*	Chemotherapy	8	28	8	62
	XRT	18	62	8	62
	Hormones	18	62	5	38
	Radioisotopes	0	0	0	0
	Surgery	14	48	7	54
	Bisphosphonates	7	24	5	38

*Patients received more than one type of treatment

Table 46. Differences between responders and non-responders

		R (n=29)				*NR (n=13)*			
		Visit 1		**Visit 2**		**Visit 1**		**Visit 2**	
		No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
ECOG PS	0	8	28	11	38	2	15	2	15
(%)	1	13	45	15	52	10	77	8	62
	2	8	28	2	7	1	8	1	8
	3	0	0	1	3	0	0	2	15
Current	Chemo	2	7	6	21	3	23	6	46
Treatment*	XRT	29	100	3	10	13	100	3	23
	Hormones	23	79	21	72	5	38	5	38
	Radioisotope	1	3	0	0	0	0	0	0
	Surgery	0	0	1	3	0	0	0	0
	Bisphosph	11	38	13	45	8	62	9	69
Analgesia*	Simple	7	24	10	34	4	31	3	23
	Weak opioid	14	48	9	31	8	62	3	23
	Strong opioid	12	41	14	48	3	23	7	54
	NSAID	15	52	9	31	4	31	5	38
	Anticonvulsant	3	10	3	10	2	15	4	31
	Antidepressant	0	0	0	0	1	8	1	7
	Lignocaine	1	3	0	0	0	0	0	0
24hr MED	Median	24		20		24		24	
(mg)	Range	0-272		0-260		0-150		0-220	

*Patients received more than one type of treatment

8.3.2 Cognitive and Affective Results

In responders, the median worst pain score improved from seven to two, whereas in non-responders it only changed from a median of six to five. In general, significantly larger reductions in all aspects of the pain scores were seen in the responder group (Table 47).

This significant improvement in all dimensions of pain control was also seen in the MPQ for responders pre and post XRT, but not for non-responders (Table 48).

Table 47. BPI results in responders and non-responders before and after XRT

		R (n=29)		P value*	NR (n=13)		P value*	P value•
		Visit 1	Visit 2		Visit 1	Visit 2		
Worst Pain	Median	7	2	<0.001	6	5	0.64	<0.0001
	Range	2-10	0-7		1-8	1-10		
Least Pain	Median	0	0	0.004	2	0	0.34	0.97
	Range	0-5	0-3		0-5	0-6		
Average Pain	Median	4	1	<0.001	4	4	0.19	0.0051
	Range	1-10	0-4		1-7	0-7		
Now Pain	Median	2	0	<0.001	3	2	0.14	0.36
	Range	0-10	0-4		0-7	0-7		
Interference Score	Median	29	1	<0.001	25	20	0.08	0.0118
	Range	6-60	0-48		4-64	0-51		
Total BPI Score	Median	49	6	<0.001	45	30	0.06	0.0041
	Range	12-94	0-64		8-98	2-72		

* Difference between visit 1 & 2; • Difference between R & NR

Table 48. MPQ results before and after XRT in R and NR

		R (n=29)		P value*	NR (n=13)		P value*	P value•
		Visit 1	Visit 2		Visit 1	Visit 2		
Sensory Total	Median	9	2	<0.001	7	6	0.45	0.0013
	Range	1-26	0-15		2-17	0-19		
Affective Total	Median	2	0	0.002	1	1	0.48	0.0031
	Range	0-11	0-9		0-8	0-9		
Total PRI	Median	13	2	<0.001	10	7	0.82	0.0008
	Range	1-33	0-18		2-25	0-22		

* Difference between visit 1 & 2; • Difference between R & NR

Anxiety, depression, fear avoidance and catastrophizing significantly improved in responders, but not in non-responders (Table 49). In particular, the rumination subscale of the PCS showed a significant difference between the two groups when comparing the median improvement in responders after XRT with the median change after XRT in non-responders. In addition, there was a reduction in the number of high scores for anxiety and depression (i.e. patients with subscores of ≥11) in responders. The number of "cases" of anxiety reduced from four (14%) to two (7%) and depression fell from three (10%) to two (7%). In non-responders "cases" of anxiety remained unchanged (two patients (15%) pre and post XRT) and depression increased from one (8%) to three (23%). Alternatively, if patients were classified as having clinically significant emotional distress, the percentage fell from 34% to 17% in responders and 23% to 18% in non-responders.

Table 49. HADS, FAPS and PCS results before and after XRT in R and NR

		R (n=29)		P	NR (n=13)		P	P
		Visit 1	Visit 2	value*	Visit 1	Visit 2	value*	value●
HADS Anxiety	Median	5	3	0.025	4	3	0.29	0.64
	Range	0-14	0-14		1-17	0-18		
HADS Depression	Median	5	3	0.018	5	5	1.00	0.12
	Range	1-14	1-15		0-14	0-12		
Total HADS	Median	9	6	0.005	8	8	0.72	0.19
	Range	1-26	1-23		1-30	1-30		
Total FAPS	Median	60	22	<0.001	62	49	0.68	0.07
	Range	4-111	0-101		5-109	0-111		
PCS Rumination	Median	3	0	0.003	1	1	0.91	0.01
	Range	0-16	0-16		0-14	0-16		
PCS Magnification	Median	2	1	0.061	2	1	0.24	0.63
	Range	0-8	0-12		0-8	0-8		
PCS Helplessness	Median	2	0	0.011	2	1	0.68	0.13
	Range	0-20	0-13		0-14	0-11		
Total PCS	Median	7	2	0.003	5	3	0.54	0.06
	Range	0-42	0-38		0-34	0-35		

* Difference between visit 1 & 2; ● Difference between R & NR

8.3.3 QST Results

Although the response to mechanical stimuli did change for a number of patients, no statistically significant differences were seen after XRT for pain scores secondary to pin prick and wind up at any site in responders and non-responders (Table 50). Thus, dynamic mechanical allodynia resolved after XRT in all patients that had it, (one (3%) responder and one (8%) non-responder). However, prior to XRT a statistically significant difference between the CIBP and control sites were seen for both pin prick VAS ($p=0.048$) and wind up VAS ($p=0.008$) in responders, suggesting a link between altered sensation and response to treatment. In non-responders, no difference was seen between the CIBP and control site for pain due to pin prick ($p=0.45$) and wind up ($p=0.17$).

No difference was seen after XRT for either MDT or MPT in responders, although for MPT the median VAS score at the CIBP site improved after XRT from four (1-9) to two (0-9) in responders ($p=0.041$). In non-responders, no significant differences after XRT were seen for pain ratings with von Frey filament testing. However, differences in pressure thresholds were seen: MDT changed significantly in non-responders at the control site (p=0.017) and MPT changed at both the control (p=0.041) and CIBP sites (p=0.037) after XRT (Table 51).

Table 50. Pin prick and wind up results in responders and non-responders

		R (n=29)				*NR (n=13)*			
		Visit 1		**Visit 2**		**Visit 1**		**Visit 2**	
		CIBP	**Control**	**CIBP**	**Control**	**CIBP**	**Control**	**CIBP**	**Control**
Pin prick % Painful		83	69	52	41	69	62	38	31
Pin prick	Median	2*	1*	1	0	2	1	0	0
VAS	Range	0-9	0-7	0-9	0-8	0-7	0-6	0-4	0-4
Wind up % Painful		76	62	62	52	69	62	46	46
Wind up	Median	3	1	1	1	2	2	0	0
VAS	Range	0-9	0-7	0-9	0-8	0-7	0-6	0-7	0-5
Wind up	Median	1*	1*	1	1	1	1	1	1
Ratio	Range	0-2	0-4	0-2	0-2	0.7-1.5	0.2-2	0-1.3	1-1

* Significant difference between CIBP & Control

Table 51. Median (Range) MDT and MPT and pain ratings

		R (n=29)				*NR (n=13)*			
		Visit 1		**Visit 2**		**Visit 1**		**Visit 2**	
		CIBP	**Control**	**CIBP**	**Control**	**CIBP**	**Control**	**CIBP**	**Control**
MDT	Median	7.3	6.8	7.3	7.3	7.3	7.3**	14.1	14.1**
	Range	1.7-31.6	1.7-25	3.3-25	3.3-17.5	3.3-25	4.5-17.5	4.5-39.1	6.8-25
MDT	Median	0	0	0	0	0	0	0	0
VAS	Range	0-3	0	0-1	0-2	0-4	0-2	0	0
MPT	Median	31.6*	57.8*	31.6	39.1	57.8**	57.8**	72.5**	57.1**
	Range	7.3-96.1	17.5-96.1	7.3-137.3	7.3-137.3	14.1-84.4	17.5 -96.1	25-137.3	17.5-137.3
MPT	Median	4**	3	2**	2	3	3	3	3
VAS	Range	1-9	1-9	0-9	0-8	1-8	1-7	0-8	0-7

* Significant difference between CIBP & Control
** Significant difference pre & post XRT

Cold allodynia (to 25°C) was present in two (7%) responders before and after XRT and in one patient (8%) increasing to three patients (23%) in non-responders. There was no significant difference between the median VAS score change between the groups (median VAS of zero at CIBP and control sites in responders and non-responders). Warm allodynia fell from 17% (five patients) to 3% (one patient) in responders and from 23% (three patients) to 15% (two patients) in non-responders, with no significant difference between the median VAS score change between the groups (median VAS of zero at CIBP and control sites in responders and non-responders).

Overall, XRT did result in alterations in response to evoked stimuli in the responder group, probably reflecting alterations in nociceptive processing (Table 52). There were a greater number of patients where sensation returned to normal after XRT in the responder group, whereas this only occurred for brush and pin prick in the non-responder group, with fewer patients having normal thermal (cool and warm) and pain summation (wind up). A small group of the responders (n=5) had normalisation of multiple QST parameters (warm, cool, pin prick and wind up) after XRT. The few patients, who had normal sensation pre XRT which then became abnormal after XRT, were not necessarily the same individuals for each QST modality. However, proportionally more of these were non-responders.

Table 52. Change in sensation at CIBP site before and after XRT in R and NR

		R (n=29)				***NR (n=13)***			
		Visit 1		**Visit 2**		**Visit 1**		**Visit 2**	
		No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Brush	Normal	15	52	22	76	6	46	8	62
	Reduced	4	14	3	10	6	46	3	23
	Increased	10	34	4	14	1	8	2	15
Cool	Normal	3	10	13	45	5	38	4	31
	Reduced	12	41	5	17	3	23	1	8
	Increased	14	48	11	38	5	38	8	62
Warm	Normal	6	21	14	48	6	46	5	38
	Reduced	6	21	5	17	2	15	3	23
	Increased	17	59	10	34	5	38	5	38
Pin prick	Normal	9	31	17	59	3	23	6	46
	Reduced	4	14	5	17	4	31	3	23
	Increased	16	55	7	24	6	46	4	31
Wind up	Normal	11	38	14	48	6	46	5	38
	Reduced	3	10	5	17	2	15	4	31
	Increased	15	52	10	34	5	38	4	31

There may be potential predictive value of QST for response to XRT, as patients who had a combination of altered sensation to thermal (warm and cool), pin prick and wind up showed the greatest reduction in worst pain score on the BPI (Table 53). The odds ratios for the baseline QST data comparing responders and non-responders are shown in Table 54.

Table 53. Response after XRT according to QST sensation at baseline

	Abnormal sensation at v1		***Normal sensation at v1***		
	Number of Pts	**Median difference in worst BPI**	**Number of Pts**	**Median difference in worst BPI**	**P value**
Brush	21	3	21	3	0.45
Cool	34	3	8	1.5	0.0344
Warm	30	3	12	1.5	0.0247
PP	30	3.5	12	3	0.35
WU	25	3	17	3	0.24
Warm & cool	26	3.5	16	2	0.0097
Warm & WU	22	4.5	20	2.5	0.0143
Cool & WU	20	5	22	2	0.0056
Warm & cool & WU	19	5	23	2	0.0014
Warm & cool & WU & PP	17	5	25	2	0.0010

PP = pin prick; WU = wind up

Univariate and multivariate analyses were performed to explore potential predictors of response to XRT. For brush, warm, cool, pin prick and wind up, the data were included in two ways: with three levels (normal, reduced and increased) and with two levels (normal vs abnormal). In the univariate analysis, QST brush was significant (on 3 levels, $p=0.039$). QST cool was significant on 2 levels ($p=0.032$), but not on 3 levels (0.093). Warm sensation was not predictive in the univariate analysis. In the multivariate analysis, cool sensation was an independent predictor of response to XRT for CIBP (on 2 levels, $p=0.032$).

Table 54. Odds ratios for baseline QST data comparing R & NR

	Sensation	*Responders (n=29)*	*Non-responders (n=13)*	*Odds Ratio*	*95% CI*
Brush	Normal	15 (71%)	6 (29%)	1.0	Reference
	Reduced	4 (40%)	6 (60%)	0.27	0.05 to 1.30
	Increased	10 (91%)	1 (9%)	4.00	0.42 to 38.5
	Abnormal*	14 (67%)	7 (33%)	0.80	0.22 to 2.97
Cool	Normal	3 (37%)	5 (63%)	1.0	Reference
	Reduced	12 (80%)	3 (20%)	6.67	0.99 to 45.0
	Increased	14 (74%)	5 (26%)	4.67	0.80 to 27.1
	Abnormal*	26 (76%)	8 (24%)	5.42	1.05 to 27.8
Warm	Normal	6 (50%)	6 (50%)	1.0	Reference
	Reduced	6 (75%)	2 (25%)	3.00	0.42 to 21.3
	Increased	17 (77%)	5 (23%)	3.40	0.75 to 15.4
	Abnormal*	23 (77%)	7 (23%)	3.29	0.80 to 13.5
Pin Prick	Normal	9 (75%)	3 (25%)	1.0	Reference
	Reduced	4 (50%)	4 (50%)	0.33	0.05 to 2.24
	Increased	16 (73%)	6 (27%)	0.89	0.18 to 4.44
	Abnormal*	20 (67%)	10 (33%)	0.67	0.15 to 3.02
Wind Up	Normal	11 (65%)	6 (35%)	1.0	Reference
	Reduced	3 (60%)	2 (40%)	0.82	0.11 to 6.34
	Increased	15 (75%)	5 (25%)	1.64	0.40 to 6.76
	Abnormal*	18 (72%)	7 (28%)	1.40	0.37 to 5.27

* 'Abnormal' defined as Reduced or Increased; CI = confidence interval

8.3.4 Functional Assessment Results

Using the GAITRite walkway to compare function before and after XRT demonstrated no significant difference after treatment in either responders or non-responders. In addition, no differences were noted when comparing the two groups (Table 55). The same was true for the activity meter results (Table 56).

Early findings using these functional assessment tools after XRT were presented by the author in poster format at the 2008 NCRI Cancer Conference in Birmingham (see Appendix) (298).

Table 55. Gait before & after XRT in responders & non-responders

		Responders n=27		***Non-responders n=13***		***P value****
		Visit 1	**Visit 2**	**Visit 1**	**Visit 2**	
Velocity (cm/s)	Median	88.1	90.4	84.1	85.1	0.40
	Range	36.4-142.5	37.3-150.7	51-151.4	31.6-111.7	
Cadence (steps/min)	Median	100.4	103.8	96.8	98.1	0.23
	Range	52.2-128.3	71.7-126.3	82.5-116.3	66.1-98.1	
FP Score	Median	85	87	86	85	0.74
	Range	56-100	53-100	65-99	56-97	

* Difference between responders and non-responders

Table 56. Activity before & after XRT in responders & non-responders

		Responders n=28		***Non-responders n=13***		***P value****
		Visit 1	**Visit 2**	**Visit 1**	**Visit 2**	
Daily hours sit/lying	Median	19.7	19.6	19.7	20.4	0.19
	Range	16.5-23.8	14.7-23.8	18.5-22.9	18.3-23.8	
Daily hours standing	Median	3.2	3	3.3	2.8	0.18
	Range	0.1-5.5	0.1-7.5	0.8-4.6	0.2-4	
Daily hours stepping	Median	0.9	1	0.9	0.9	0.93
	Range	0.03-2.3	0.02-2.9	0.3-1.9	0-3.7	
Daily hours up	Median	4.3	4.4	4.3	3.6	0.28
	Range	0.2-7.5	0.2-9.3	1.1-5.5	0.2-7.7	
Energy expenditure (MET/hr)	Median	32.2	32.4	32.1	31.9	0.11
	Range	30.2-35.3	30.1-35.9	30.7-34.2	30.1-33.8	
Daily number of steps	Median	4345	4688	3922	3863	0.29
	Range	92-12225	136-13623	1318-9210	186-7935	
Daily number of transitions	Median	41.5	38.5	49	46	0.86
	Range	14-66	9-73	23-83	7-65	

* Difference between responders and non-responders

In addition to comparing those patients who completed two assessments and dropouts (Chapter 7), a sensitivity analysis was performed to examine any differences in those patients who responded to treatment (n=29) and all other patients (n=31), i.e. those patients who didn't respond (n=13) or who dropped out (n=18). The only variables which were significant in this univariate analysis were some of the activity meter results: daily hours stepping ($p=0.019$), energy expenditure ($p=0.022$) and daily number of steps ($p=0.019$). In the multivariate analysis, daily hours stepping was the most significant, and the other measures did not add to this.

8.4 Discussion

Using worst pain to classify patients as having an analgesic response to palliative XRT 6-8 weeks after treatment showed a response rate of 69% in evaluable patients. This equates to a 48% response rate when assessed by intention to treat. This compares well with previously published work. Using the BPI as a measure of response, rates of 66% (160, 162) and 72% (120) have been quoted in evaluable patients. When assessed by intention to treat, the rates in these studies were 32% (160, 162) and 36% (120) respectively. Larger studies and systematic reviews have generally found lower response rates, mainly due to the varying definitions of response in the literature (7, 112, 113, 116). With this in mind, caution should be taken when reviewing response rates, especially with regards to whether the assessment has been presented on the intention-to-treat principle, so that results are not misleading.

In the current work, as well as reductions in pain, benefits were seen in cognition and affect after XRT. Anxiety, depression, fear avoidance and catastrophizing improved significantly in those with an analgesic response to treatment compared with non-responders.

Although the cognitive and affective components of CIBP improved in parallel with treatment, objective measures of function did not change. As described in previous chapters, this may be because of a lack of sensitivity and specificity, confounding factors or the size of the study. Therefore, although these measures were useful to help confirm the frailty of the population in comparison with healthy individuals and to aid prediction of those patients unlikely to complete follow up, they were not useful to measure response to treatment. This statement assumes that function should improve with XRT, but it may also be the case that XRT for CIBP does not improve functional outcome and in fact the measures were accurate. Others studies (not specifically in CIBP) have demonstrated that pain intensity and physical functioning may be only modestly associated (299). For example, some patients may limit their physical activity as pain increases, and their response to reduced pain may be to increase their activity until pain increases to its tolerated intensity. Other patients will tolerate increased pain to maintain a desired level of function and their response to pain improvement is to report less pain as long as their level of function remains satisfactory (159). Unfortunately, to date, the literature examining objective functional response to XRT is limited. Niewald et al., in a study of 100 patients with CIBP, reported that mobility was severely impaired in 62% of patients prior to treatment (163). Patients were then divided into two groups and treated with either "rapid course" or "more standard" XRT. Improvement in mobility was experienced immediately after XRT in 70% and 71% of patients respectively. Mobility remained improved in 26% and 24% at the final follow up (median follow up of 12 months). These findings imply that XRT does impact on function, but mobility status was assessed using a subjective scale (none, slight, moderate, severe). Safwat et al. also used a four point subjective scale of mobility before and after XRT and found a significant improvement after treatment with 20Gy in 5 fractions and 8Gy in a single fraction, but not with 30Gy in 10 fractions (300). Further work in this area to clarify the situation is warranted. This has been reinforced in work by Barton et al., in which important patient-based outcomes were evaluated specific to XRT for CIBP (301). Patient interviews and survey showed that chronic pain and associated limitation of movement were the disease symptoms causing the most concern. In addition, physical functioning is one of the key outcome domains recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) as a core component of health-related quality of life that should be assessed in all clinical trials of chronic pain (302).

Health-related quality of life is "a subjective, multi-dimensional construct reflecting functional status, psychosocial well-being, health perceptions, disease and treatment-related symptoms from the perspective of the patient. It incorporates expectation, satisfaction, value system and many aspects of a patient's life" (303). In view of this, IMMPACT recommended a further five core outcome domains that are pertinent to characterise adequately the impact of an intervention for chronic pain. These include assessment of pain, emotional functioning (a core component alongside physical functioning), participant ratings of improvement and satisfaction of treatment, symptoms and adverse effects, and participant disposition (302). Biological biomarkers (such as assessment based QST) were considered as a supplemental domain for consideration. The relevance of each domain may vary according to the stage of illness, treatment, age and cultural background. IMMPACT have subsequently published recommendations for core outcome measures for each domain (e.g. use of the functional interference BPI items to assess physical functioning and the SF-MPQ to assess the sensory and affective qualities of pain), also taking into consideration what change is important clinically for patients and what difference in magnitude of response is large enough to establish the scientific or therapeutic importance of the results (158, 159). In addition, they caution the fact that when testing multiple outcomes, the statistical power of a trial may be adequate for the primary endpoint, and therefore inadequate power may sometimes explain non-significant secondary outcome measures (159). Turk et al. also consider the fact that assessment of multiple outcomes, such as those completed in the current study, will inevitably require more effort from participants than simply assessing pain reduction as the sole endpoint, and hence patient burden is a concern. However, as demonstrated in the current work, there are relatively brief measures which are acceptable to participants and can adequately capture the domains described (302).

Chow et al. has recently highlighted that quality of life may be the most relevant endpoint in patients with bony metastases, although this is not reflected in previous clinical trials which have focused largely on objective endpoints such as analgesic consumption, hypercalcaemia, pathological fracture and spinal cord compression (303). With this in mind, the International Bone Consensus Working Party has recommended developing a bone metastases-specific quality of life instrument since publication of the consensus in 2002 (115). This is important as bone metastases-specific quality of life instruments are lacking and these issues are vital to aid patients when deciding on treatment options for CIBP. They proposed a module specific to patients with bone metastases to be given concurrently with the core European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ). The aim was to address: (A) disease symptoms related to bone metastases; (B) side effects and complications; (C) additional quality of life dimensions relevant across diagnosis and treatment. It was to be assessed in various settings, such as in patients receiving XRT, systemic therapy, orthopaedic treatment and symptom control (303).

To develop this further, Harris et al. published work in 2009 examining the agreement between health care professionals' and patients' evaluation of the health-related quality of life issues for patients with bony metastases (304). Four hundred and thirteen patients and 152 health care professionals were interviewed. Mean scores reported by professionals were almost always higher than patients, with the greatest difference observed for items related to pain. Both patients and professionals agreed that four quality of life items affected bone metastases patients profoundly: long term (chronic) pain, difficulty carrying out daily tasks, ability to perform self care, and ability to perform role functioning. Professionals ranked items related to symptoms and treatment side effects as more important to patients, with an emphasis on issues relating to pain. Patients focused on psychosocial items and included three "worry issues" (dependency on others, loss of mobility compromising independence, and disease progression, deterioration in condition and future complications). The authors comment that both subjective and objective perspectives are important, but may be difficult to elicit, as only 26% of respondents used formal quality of life questionnaires in their practice and patients' concerns regarding psychosocial matters were often not raised (304).

The EORTC QLQ-BM22 has now been developed (305). This is the bone metastases module to supplement the EORTC QLQ-C30. To ensure the validity and reliability, its development was done in phases including generation of the health-related quality of life issues, questionnaire construction, and testing for acceptability and relevance. It contains 22 items conceptualised into both symptom scales (with five painful site questions and three pain characteristics questions) and functional scales (with eight functional interference and six psychosocial aspects) (305). Further development is now required involving administration in a large multi-cultural population in clinical trials to provide data on the psychometric properties.

The fact that the EORTC QLQ-BM22 questionnaire concentrates on pain characterisation, function and psychosocial aspects of bony metastases reaffirms the focus of the current study.

8.4.1 Predictors of Response to Radiotherapy for CIBP

Abnormal cool sensation at the site of CIBP was independently predictive of a response to XRT in the multivariate analysis. This is an encouraging finding especially in a study with relatively small numbers. However, it reflects what was suggested in the pilot work. Altered thermal processing may mirror the underlying pathophysiological changes occurring at the level of the spinal cord, and hence may be a potential biomarker of analgesic response. It is important to take this foward in future work, with a focus on warm and cool sensitivity in a much larger number of patients with CIBP. It may also be of value to adapt the QST paradigm to allow assessment of specific thermal thresholds, rather than using two distinct measures of temperature. Although relationships were found between analgesic response to XRT and psychological factors, none of these were independently predictive in the multivariate analysis.

It has been suggested that patients undergoing palliative XRT may provide new opportunities for the development of predictive XRT biomarkers (272). Despite this, very little work has been carried out in the literarure examining predictors of response to XRT for CIBP. However, a number of authors have looked at prognostic factors. It is important to differentiate between the two; a prognostic factor is any measurement available at initial assessment that correlates with disease-free or overall survival, and as a result, is able to correlate with the natural history of the disease. In contrast, a predictive factor is any measurement associated with response to a given therapy. Some factors may be both prognostic and predictive. Tong et al. showed that initial pain score and site of the primary lesion were important prognosticators (7). Janjan highlighted that the site of the primary cancer, the interval between primary diagnosis and development of metastases, the number and distribution of bony metastases and performance status were all prognostic factors (306). Relationships have also been shown between urinary n-telopeptide of type 1 collagen (NTX) and skeletal events, progression in bone and death in patients with bony metastases (22, 307).

One possible predictor of response to XRT has been examined by Hoskin et al. (270). In this research, urinary markers of bone resorption (pyridinoline and deoxypyridinoline) were used to investigate the association between pain relief with XRT and the urinary marker concentrations before and after treatment in 22 patients. In the patients who did not get an analgesic response to XRT, baseline concentrations of both markers were higher than in responders, and they rose further after treatment. In responders, the mean values remained unchanged. This resulted in a significant difference between the two groups after treatment. The authors concluded that XRT-mediated inhibition of bone resorption, and thus osteoclast activity, could be a predictor for pain response (270).

Use of QST as a Predictive Tool of Response to Treatment

QST is a well recognised method of assessment in patients with diabetes. Hence, although QST has not previously been used as a predictive tool in bone pain, lessons might be learned from looking at its use in diabetic neuropathy and other diseases. For example, in the 1970s, studies suggested that QST for thermal thresholds may detect preclinical diabetic neuropathy (212). Unfortunately, this has not been confirmed in subsequent prospective studies (215). However, thermal thresholds have been shown to predict the pain severity of diabetic neuropathy (224). Because no predictors for the development of pain as a symptom of diabetic neuropathy were known, Kramer et al. examined 30 patients with signs of peripheral diabetic neuropathy with a combination of electrophysiological studies, heart rate variability testing and QST. In those with pain, the VAS ratings correlated with impairment of small fibre dysfunction. In particular, a significant positive correlation between deterioration of cold detection thresholds and intensity of pain was seen (224). Nurmmiko and Bowsher used QST to examine patients with post-herpetic neuralgia and patients with shingles not followed by neuralgia. Hypoaesthesia at the herpetic stage was found to be a predictive factor for later development of neuralgia (308). In contrast, Haanpaa et al. concluded that QST in the early stages of herpes zoster was not helpful in predicting which patients would go on to develop post-herpetic neuralgia (309).

Looking specifically at using QST as a clinical biomarker to predict response to treatment has been used in sciatica. Schiff and Eisenberg completed quantitative thermal and mechanical sensory testing in 20 patients with lumbar radiculopathy before and after epidural steroid injection (310). A significant positive correlation was found between the increase in cold sensation thresholds of the affected dermatome and the improvement in pain rating. The increase in touch and vibration thresholds was inversely correlated with pain improvement. However, in another study examining the predictive value of QST in patients treated with a lidocaine patch for painful distal neuropathy, it was not found to be helpful (311).

8.4.2 Study Limitations

One of the main disadvantages of the study described in the last few chapters was the fact that numerous variables were measured. This was necessary in order to characterise the multi-dimensional components of CIBP, but meant that analysis was difficult and less focused on one specific question. However, the fact that all the assessments were carried out by one examiner was advantageous. Another useful point was that a combination of categorical and continuous outcome measures were utilized which complement each other. This is nicely explained by Kroenke, as follows (153). Categorical outcomes may be more clinically tangible and can be collapsed into two categories (for example, responders and non-responders to a treatment, as above). This enables use of logistic regression analysis to identify predictors of outcome and associated odds ratios. Continuous measures of symptom outcome may be more sensitive in detecting smaller changes and may allow investigators to use linear regression analysis to estimate the variance in outcome uniquely attributable to specific variables.

Confounding factors also cause concern. The difficulty measuring functional outcome in relation to this has already been described. Another possible issue is peripheral neuropathy which is common in cancer patients. Other causes of neuropathy (e.g. disturbances of metabolic or endocrine origin, nutritional deficiency, infection, drugs like gabapentin, chemotherapy, paraneoplastic phenomena or coexisting disease like diabetes, or alcohol abuse) may all impact on the QST findings. Lipton et al. also demonstrated that cancer patients in general have altered QST findings (226, 227). It is not possible to control for these factors, but the results, along with the control sites used, should be considered with this in mind.

8.5 Conclusion

Patients with an analgesic response to XRT for CIBP had reductions in anxiety, depression, fear avoidance and catastrophizing and fewer were classified as having emotional distress. Thus, improvements in pain were paralleled by improvements in psychological wellbeing. Performance status also improved, although this was not reflected in the objective functional outcome measures. In addition to having an impact on cognition and affect, XRT was shown to alter response to evoked sensory stimuli, with responders more likely to have normalisation of abnormal sensation than non-responders. Those patients with altered response to thermal, pin prick and wind up stimuli showed larger reductions in pain after treatment. In particular, abnormal cool sensation was an independent predictor of analgesic response to XRT.

These findings are important in a field where biomarkers of response to treatment are lacking. In an age where targeted treatment is developing, translational research should be utilised to improve outcomes for patients. However, despite being the gold standard treatment for CIBP, there has been little work looking at individualised treatment or quality of life outcomes. Therefore, it is vital that studies are created to move this forward. A larger study is needed focusing on thermal sensory processing before and after XRT to clarify and confirm the findings in the current work. This should examine ranges of temperature rather than just 25°C and 40°C. Being able to predict which patients would benefit from XRT for CIBP would have rewards for health economics and most importantly patients.

Chapter 9 ASSESSMENT OF CIBP AT 3-4 MONTHS

9.1 *Introduction*

The last two chapters have described the main outcomes of the study which were to evaluate the response to XRT two months after treatment using a tool to address the multi-dimensional components of CIBP. One final aspect of the study was to complete a third assessment 3-4 months after treatment to assess whether the response to treatment was maintained and to identify whether the combination of assessment tools could be practically used to assess CIBP over time.

9.2 *Method*

The study criteria and tools used in this part of the work are as previously described. Patients who had completed an assessment at baseline and at 6-8 weeks were invited to undergo a third assessment at 3-4 months after XRT. This was identical to the assessment completed at the first two visits.

9.2.1 Statistical Analysis

In the analysis described in this chapter the Minitab® 15 Statistical Software package was used. Descriptive statistics were used to summarise the demographic results. The Wilcoxon signed rank test was used to analyse the changes between the baseline and the 3-4 month follow up visit, and to examine any differences between the CIBP and control site in QST. A p value of <0.05 indicated statistical significance.

9.3 *Results*

Twenty-eight patients (47%) out of the initial 60 patients who underwent a baseline assessment were able to complete a third assessment 3-4 months after XRT. This population comprised 29% men and 71% women with a median age of 64 (range 38-79) years. At this visit all patients were seen as outpatients. The proportion of patients assessed to be performance status zero was at its highest level of 36%, with

57% PS one and only 7% PS two. The proportion of patients completing three visits with prostate cancer as their primary tumour was the same as the baseline at 25%. The proportion of breast cancer patients increased to 68% in this final group and the proportion of lung cancer patients fell to only four percent. There was no significant difference in the current anti-neoplastic treatment at 6-8 weeks and 3-4 months. In this group of 28 patients, the median 24 hour equivalent morphine dose increased from 20.5mg (range 0-150mg) at the baseline visit to 32mg (0-360mg) at the final assessment ($p=0.037$). Cognitive and affective assessment scores remained low and generally improved further between the second and third assessments as shown in Table 57. The pattern seen at 3-4 months was very similar to that seen at 6-8 weeks, with statistically significant improvements in pain, mood, fear avoidance and catastrophizing. Using scatterplots allowed easy visualisation of whether the results were a reflection of a constant pain status between the second and third assessment or whether there were changes in individuals with some improving and some deteriorating. As can be seen from Figure 25, the latter is generally true. Some patients with an initial benefit subsequently worsened and vice versa. Others had responded after 6-8 weeks, but improved further by the final assessment.

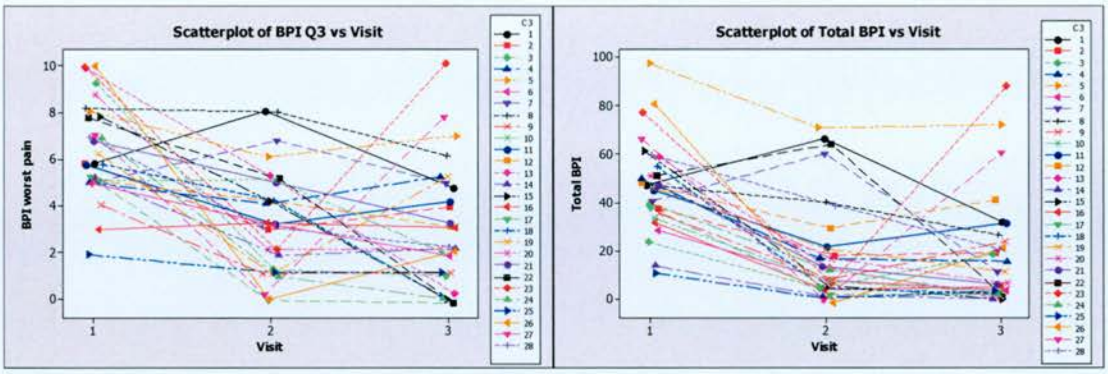
Table 57. Questionnaire results at all three assessments (n=28)

	Baseline *Median (range)*	***6-8 weeks*** *Median (range)*	***3-4 months*** *Median (range)*	***P value****
BPI Worst Pain	6 (2-10)	3 (0-8)	2 (0-10)	<0.001
BPI Functional Intereference	27.5 (6-64)	4.5 (0-51)	4 (0-50)	<0.001
Total BPI Score	48 (12-98)	11 (0-72)	10.5 (0-88)	<0.001
MPQ Sensory Total	9 (2-23)	3 (0-19)	2 (0-27)	<0.001
MPQ Affective Total	2 (0-10)	0 (0-9)	0 (0-11)	0.001
MPQ Total PRI	12 (2-32)	3 (0-22)	2 (0-38)	<0.001
HADS Anxiety	4.5 (0-16)	3 (0-14)	2.5 (0-17)	0.018
HADS Depression	4.5 (0-14)	4 (0-11)	5 (0-11)	<0.001
Total HADS	8.5 (1-30)	7 (1-25)	7 (1-28)	0.05
Total FAPS	56.5 (4-111)	26.5 (0-111)	16 (0-116)	<0.001
PCS Rumination	3 (0-14)	0 (0-16)	0 (0-16)	0.003
PCS Magnification	2 (0-8)	1 (0-12)	1 (0-11)	0.31
PCS Helplessness	2 (0-14)	1 (0-11)	0 (0-23)	0.007
Total PCS	7 (0-34)	2 (0-38)	2 (0-50)	0.004

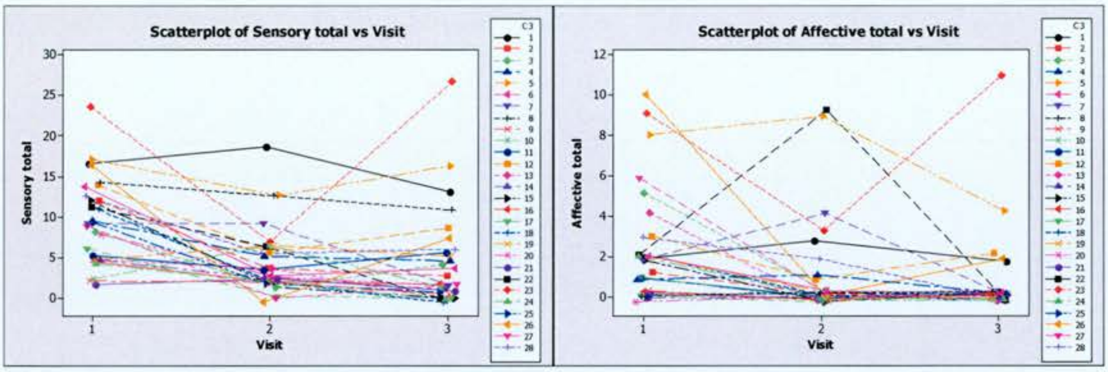
* Difference between visit 1 and visit 3

Figure 25. Questionnaire scores at baseline, 6-8 weeks and 3-4 months

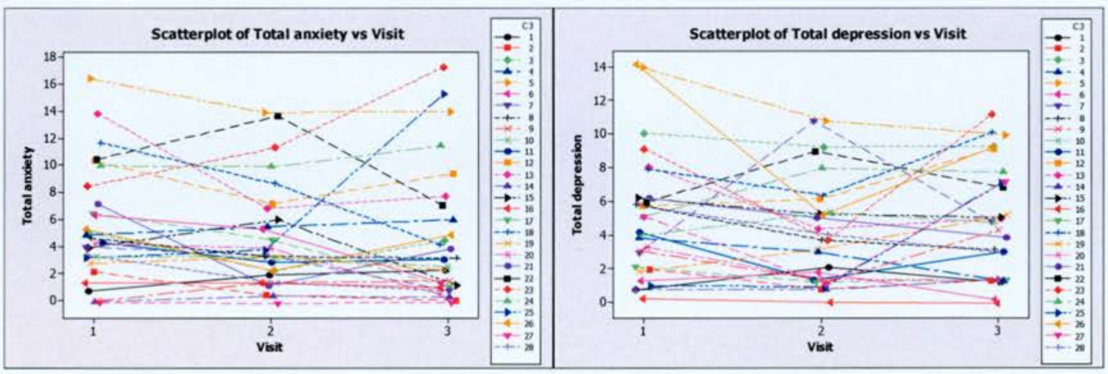
A) Worst & Total BPI scores



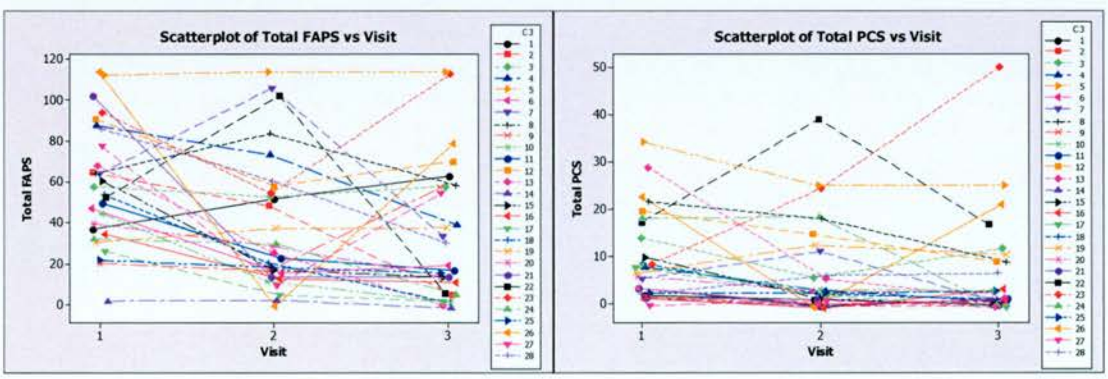
B) Sensory & Affective MPQ scores



C) Anxiety & Depression HADS scores



D) Total FAPS & PCS scores



Nineteen patients (68% of evaluable patients, 32% on intention-to-treat) had an analgesic response to XRT at the 3-4 month timepoint on the basis of a $\geq$ 30% improvement in worst BPI score. This compares with the response rate at 6-8 weeks. However, it can be seen from the scatterplots above that the clinical situation changed between the last two visits in some individuals. Further analysis revealed that 16 patients (57%) were classified as responders at both 6-8 weeks and 3-4 months. Six patients (21%) were never responders at any assessment. A further six patients had different responses at the follow up visits. Three of these were initially classified as non-responders because although their pain had not worsened at the middle assessment, the improvement was less than 30%. However, the pain improved further by the final assessment. In these three individuals the worst pain scores changed from (A) five to five to two, (B) five to four to three, and (C) seven to five to three at each visit. In the other three patients, the initial response was not maintained, with the worst pain scores changing from (A) six to one to five, (B) ten to two to ten, and (C) seven to zero to eight.

Examining the QST results in the 28 patients at the three assessment points did not reveal any additional statistically significant findings. The patterns of sensory abnormalities and changes after XRT were in agreement with those presented in the previous chapter. (Regression analysis was not performed on QST data at the 3-4 month visit.)

In a similar manner, no significant differences were found between the first and last assessment for either the GAITRite or activPAL results. XRT was not found to impact on function when measured with these tools.

Although not a formal trial endpoint, survival was investigated six months after the final study assessment. Twenty-six patients (43%) had died by this time point. Median time until death from study entry in these 26 patients was 146 (range 10-560) days. In all patients, six months after study closure, median overall survival was 313.5 (range 10-687) days, although it is appreciated that a much longer follow up period would be necessary to get a true reflection of survival in this population.

9.4 Discussion

Analysis of the data at the final visit, 3-4 months after XRT for CIBP, revealed that 68% of evaluable patients were responders (32% using intention-to-treat assessment). This was similar to the proportion of patients with a clinically significant analgesic response at the second assessment. Reflecting the fact that fitter patients were more likely to be able to attend for follow up at this later time, performance status was at its highest level seen in the study. Also as expected, the demographic of the tumour types seen at 3-4 months demonstrated the natural progression of disease, with a decreasing percentage of patients with lung cancer in this group. At the third visit, benefits were still evident in the psychological parameters, including anxiety, depression, fear avoidance and catastrophizing. However, by this stage it was clear that a group of patients had early relapse of pain. Conversely, in another group pain control continued to improve between two and four months. Nevertheless, by classifying response at 6-8 weeks, only three patients (11%) were labelled as non-responders, when in fact they were responders given more time. In a paper examining the best time to assess response to XRT in 199 patients with CIBP (discussed in Chapter 4), the proportion of those becoming a responder from a non-responder between two and three months of follow up was 18% of those evaluated (16% on intention-to-treat basis) (160). However, this was less than the difference between one and two months. These findings reflect the importance of consistency in definitions of response, as differing time points produce varying results. It could also be argued that completing a full evaluation of CIBP, including a sensory and functional assessment, after the two month timepoint would subject patients to unnecessary burden as the third visit in this study did not provide any additional information over and above that found already.

Three to four months after the baseline assessment, attrition was high with 53% of patients unable to complete an assessment. As described previously, this is one reason for measuring response at an earlier date. However, this figure is favourable in comparison to other studies at this timepoint. Hadi et al. had attrition rates of 56%

(273) and 63% (274) at three months in two separate studies and Li et al. had a dropout rate of 60% at three months (160).

9.5 Conclusion

These are interesting data which confirm the continued response of XRT for CIBP in the majority of patients, but the results highlight the fragility of others and the dynamic nature of bone pain. This supports the potential improved response of some primary tumours, but is also a reflection of general disease. Although not proof of a causal relationship between pain and psychological factors, it was encouraging that the improvements in cognition and affect were ongoing. However, significantly longer follow up is required to be able to explore these relationships further. This is important for improved quality of life for patients with CIBP who are now living for longer with metastatic disease.

Chapter 10 DISCUSSION

The intention of this research was to increase the knowledge and understanding of CIBP to allow selection of the most appropriate treatment for the patient, targeted to help their specific needs. The aims of the research presented in this thesis were:

1. To summarise current understanding of the pathophysiology, epidemiology, clinical features, assessment and management of malignant bone disease and CIBP.
2. To characterise CIBP using quantitative sensory testing (QST) as a measure of altered sensory processing.
3. To establish systematically the sensory, cognitive, affective and functional components of CIBP to develop a comprehensive assessment tool.
4. To explore whether clinical biomarkers can be developed to aid prediction of response to treatment for CIBP, in particular XRT.

This chapter focuses on these aims to establish whether they were achieved and discusses how this work could be developed in the future.

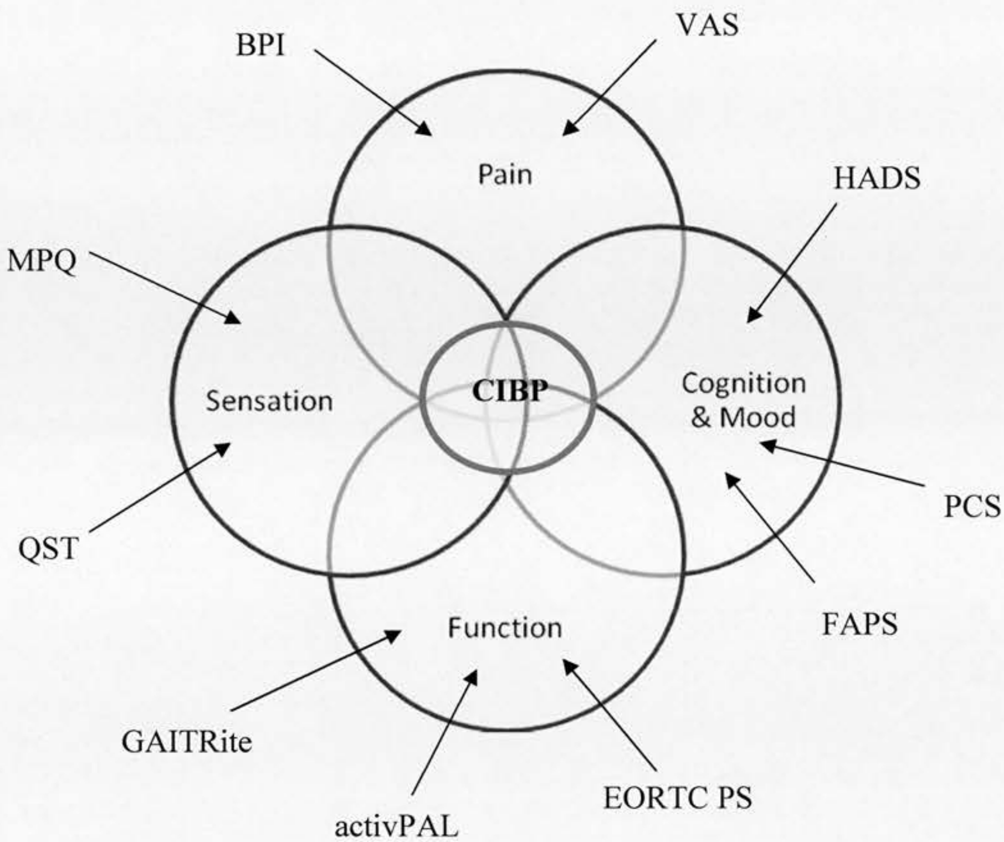
10.1 CIBP Literature Review

CIBP is common, poorly understood and undertreated. A number of key issues are clear from reviewing the literature. Firstly animal models have highlighted the importance of the dorsal horn of the spinal cord in CIBP pathophysiology. It is vital to appreciate that it is unique from solely inflammatory or neuropathic pain. Understanding the mechanisms leading to peripheral and central sensitisation will hopefully guide management of CIBP and lead to the investigation of novel treatments.

It is also important to appreciate the clinical qualities of CIBP. By recognising particular features of pain, such as the impact of breakthrough pain, treatment can be developed to try to mirror the temporal characteristics. With this in mind, the literature has highlighted the value of measuring the worst pain score. It is also recognised that pain does not occur in isolation. Depression is common with cancer pain, as is functional impairment, all of which have a negative impact on quality of life. In conjunction with this, pain control remains suboptimal despite the vast armamentarium of treatment options, including gold-standard XRT. However, it is apparent that inadequate pain management is not solely due to poor treatment efficacy. Deficient pain assessment and a lack of a standardised approach are also to blame. As patients are now potentially living with bony metastases for years, this is an issue which needs addressed in order to improve CIBP management and quality of life.

Review of the literature has shown that gaps exist in CIBP research. There is a general lack of studies exploring the multi-dimensional components of CIBP and its characterisation. There is poor agreement on the best tools to use for CIBP assessment. In addition, clinical predictors of response to treatment are absent. Thus, the literature review reinforced the need to study the cognitive, affective, functional and sensory aspects of CIBP and to address the lack of biomarkers in this area. With this in mind, Figure 26 shows which tools were utilised in the main study to address these aims.

Figure 26. Assessment tools used to characterise CIBP



10.2 Sensory Characterisation of CIBP using QST

QST was overwhelmingly the most sensitive test used in patients with CIBP with potential clinical utility. It was used, not only to characterise CIBP, but to assess response to treatment and also as a possible predictor of response to XRT. In all three respects it was felt to be of value. Its use as a clinical biomarker will be discussed further later in the chapter, but prior to this it is useful to compare the QST results together to look for consistencies. In this way, the possible strengths and weakness can be highlighted. For example, Table 58 shows consistently that more than half of patients at baseline had abnormal sensitivity to brush, warm, cool, pin prick and wind up stimuli at the CIBP site in comparison to the control area. In the majority, the sensitivity was increased, although a smaller proportion did have reduced sensation to the stimuli. Although, not shown in the table, stimuli were associated with pain at the CIBP site in a proportion of patients and the percentage finding this painful was higher than at the control site. However, the difference using the VAS was usually not significant. The only consistent significant finding with regards to the VAS was with cool sensation. It appears that the quality of the sensation is of more value to record than the pain intensity related to the sensation. The table also highlights the discrepancies using the von Frey filaments to assess mechanical detection and pain thresholds. Although significant differences in thresholds were found, the direction of the change was not constant. In theory, it would be expected that the CIBP site would be more sensitive to pain and hence have an increased threshold. This was seen with suprathreshold in Chapter 5 and MPT in Chapter 6, but was not seen with MPT in Chapter 5.

Table 58. Baseline QST results

	Baseline (Pre XRT) CIBP in comparison with control							
	Chapter 5				**Chapter 6**			
	% AbN	**Sensitivity**	**T**	**VAS**	**% AbN**	**Sensitivity**	**T**	**VAS**
Brush	53%	Majority ↑	-	-	55%	Majority ↑	-	NS
MDT	73%	-	NS	-	78%	-	NS	NS
MPT	64%	-	Sig ↑	-	77%	-	Sig ↓	NS
SupraT	38%	-	Sig ↓	Sig ↑	-	-	-	-
Warm	69%	Majority ↑	-	Sig ↑	77%	Majority ↑	-	NS
Cool	58%	Majority ↑	-	Sig ↑	83%	Majority ↑	-	Sig ↑
Pin prick	52%	Majority ↑	-	-	70%	Majority ↑	-	NS
Wind up	-	-	-	-	60%	Majority ↑	-	Sig ↑

AbN = Abnormal; T = Threshold; Sig = Significant; NS = Not significant; " – " = Not Tested

After XRT a number of themes can also be identified when looking at the QST results in all the studies together. Prior to identifying patients as responders or non-responders, the percentage of patients with abnormal sensitivity to all the stimuli reduced after XRT (Table 59). The same was true for responders in Chapter 5 (not shown in table) and in Chapter 8. More responders had normalisation of sensation to brush, warm, cool, pin prick and wind up at the CIBP site after treatment. In non-responders, fewer patients had normalisation of altered sensation, and for brush, cool and wind up the percentage of patients with abnormal sensation increased (Table 59). As with the findings at the baseline assessment, inconsistencies were seen using von Frey filaments to assess response to XRT. Theoretically, after XRT it would be expected that mechanical pain threshold should increase (i.e. reducing sensitivity), as shown in animal models (290). Hence, pain threshold should increase in responders and decrease or remain unchanged in non-responders. This was not seen across all the studies (Table 60).

Table 59. QST results after XRT

	Post XRT											
	Chapter 5 (All patients)			Chapter 7 (All patients)			Chapter 8					
							R			NR		
	AbN pre	AbN post	VAS	AbN pre	AbN post	VAS	AbN pre	AbN post	VAS	AbN pre	AbN post	VAS
Brush	35%	30%	NS	50%	29%	NS	48%	24%	NS	54%	62%	NS
Warm	61%	39%	NS	71%	55%	NS	79%	52%	NS	54%	62%	NS
Cool	43%	26%	NS	81%	60%	NS	91%	55%	NS	62%	69%	NS
Pin prick	55%	23%	-	71%	45%	Sig ↓	69%	41%	NS	62%	52%	NS
Wind up	-	-	-	60%	55%	NS	62%	52%	NS	54%	62%	NS

R = Responder; NR = Non-responder; AbN = Abnormal; Sig = Significant; NS = Not significant; " – " = Not Tested

Table 60. von Frey QST results after XRT

	Post XRT									
	Chapter 5				Chapter 7		Chapter 8			
	R		NR		All Patients		R		NR	
	T	VAS	T	VAS	T	VAS	T	VAS	T	VAS
MDT	NS	-	Sig ↑	-	NS	NS	NS	NS	NS	NS
MPT	Sig ↑	-	Sig ↑	-	NS	NS	NS	NS	Sig ↑	NS
SupraT	NS	NS	NS	NS	-	-	-	-	-	-

R = Responder; NR = Non-responder; T = Threshold; Sig = Significant; NS = Not significant; " – " = Not Tested

It is also clear from looking at Tables 59 and 60 that VAS did not change significantly after XRT in nearly all the parameters. As with the baseline data, this possibly reflects the importance of the sensation quality rather than the pain intensity in QST. Lastly, wind up was not found to be statistically significant and overall was not felt to be helpful in this work.

Therefore, using QST to characterise CIBP was possible and a number of clear themes were identified. However, it is also evident that the further work in this area is needed and the QST paradigm requires more thought.

10.3 Development of a Multi-Dimensional CIBP Assessment Tool

A multi-dimensional CIBP instrument would include QST as discussed above. The importance of the questionnaires and functional assessment tools in this regard are now considered.

10.3.1 Value of Questionnaires to Assess CIBP

Despite being a frail population with advanced malignancy and pain, all patients completed the five questionnaires and this seemed acceptable to the group.

Using the BPI to assess CIBP confirmed the temporal variability of CIBP and the importance of measuring worst pain score, highlighting the issue of breakthrough pain and the need to treat it effectively. Consistently worst pain was a few points higher than average pain or pain right now. At the baseline assessment, the BPI also demonstrated the influence of CIBP on functional activities. In particular, it demonstrated a detrimental effect on general activity, normal work, walking and enjoyment of life. In the group as a whole after XRT, pain significantly improved as measured with the BPI. In conjunction with reductions in worst pain score, benefits were seen in the functional interference items. When patients were classified as responders or non-responders according to their worst pain score after XRT, patterns were seen. All aspects of pain and functional interference improved in responders, but less improvement was seen in non-responders.

When the available literature using the BPI to assess CIBP was reviewed, the results in the current study were comparable. It was noted that if patients had more than one site of pain, then they were asked to attribute how much that particular pain interfered with the functional interference items and to ignore the relative contribution of other pains. This was easier for some patients than others. However, this was the only particular issue of concern with its use. The shortened length of the version used was felt to be appropriate and overall the BPI was felt to be of benefit in the study.

The MPQ allowed quantification of the patients' subjective pain experience with the use of pain descriptors. After XRT, both the affective and sensory scores statistically significantly improved with patients using fewer descriptors at lower pain intensities. This was also true for patients who responded to XRT, but there was no significant change in non-responders. Patients generally appeared to understand how the complete the questionnaire with instruction from the author. However, certain words seemed difficult for some patients to understand. In particular, patients queried the meaning of the word "splitting". This perhaps reflects its development in students rather than patients. Although it was useful to appreciate the words patients use to describe their pain, the sensory aspects of CIBP were also assessed by QST and the affective component was assessed by the HADS questionnaire. In addition, the PPI was assessed by present pain in the BPI and the VAS part of the MPQ, although interesting in the analysis, was duplication. Hence, overall the MPQ was not of unique merit to this work.

The HADS scores were felt to be surprising low, but despite this, the questionnaire classified 23% of patients with CIBP as being borderline or cases of anxiety and 33% fitted this definition for depression using the original definitions in the literature (181). Thirty-three percent of patients were felt to have clinically significant emotional distress before XRT. In the group overall, anxiety and depression scores improved after XRT and fewer patients were classified as being emotionally distressed. When patients were subsequently classified according to their response to treatment, anxiety and depression scores were significantly better in responders and not in non-responders. Fewer responders were classified as cases of anxiety, depression or emotional distress. There were no major issues when patients completed the questionnaire, although as described in the literature, question eight was not of particular benefit due to its lack of discriminatory power in cancer patients (189).

It was difficult to judge the success of the use of the FAPS as there was little in the literature with which to compare the results. As with the HADS, scores appeared to be low, but the questionnaire was useful to detect that a large proportion of patients with CIBP were unsure about what activities they should or should not be doing in relation to their pain. This is of concern and may reflect inadequacies on our behalf as clinicians in discussion with patients. Thus, patient education is vital to help reduce fear avoidance behaviour and may be especially important for simple activities of daily living. Despite having low scores at the baseline assessment, there was a statistically significant reduction in FAPS score after XRT. Further analysis showed that this was only true for responders. As with the FAPS, comparisons with previous studies were difficult for the PCS. Again scores were generally low, but it did allow identification of catastrophizers. In individuals who ruminate and magnify their pain and adopt a more helpless role, education and perhaps psychological input may be worth considering to improve quality of life. After XRT, all dimensions of pain catastrophizing improved. The improvement was significant in responders to treatment, but not to non-responders.

Use of the FAPS and the PCS did not cause any significant difficulty. Although the FAPS on first impression does look rather arduous, patients appeared to find it acceptable. The patient group seemed to understand the phrases and responded appropriately. However, one criticism has already been mentioned and this relates to what the questionnaires are measuring. Are they measuring a true psychological problem due to pain or do they simply reflect patients' underlying disposition? An argument against this is that both improved with successful treatment of pain. Another issue is whether the questionnaires, in particular the PCS, may simply be mirroring pain intensity. For example if the PCS score is reduced with an intervention for pain, is this reflecting a reduction in pain intensity or a true reduction in catastrophizing behaviour? Further use of these types of questionnaire would be of value to try to clarify these issues.

Lastly, although the VAS was generally felt to be an appropriate tool to use and patients appeared to find it acceptable, in retrospect some patients seemed to find the NRS in the BPI easier to complete. This is in agreement with the available literature (167); it is more practical than the VAS, easier to understand for most people, and does not require clear vision, dexterity, paper and pen. It also has the advantage of being useable during a telephone interview if this was required in either a research or clinical setting. Therefore in future studies, the NRS would be a better method to record pain intensity, for example, during QST assessment.

In summary, the five questionnaires provided a baseline characterisation of the cognitive and affective aspects of CIBP and highlighted psychological issues which potentially would otherwise have gone unrecognised. In addition, they were able to demonstrate changes after XRT, with reductions in pain and improvements in anxiety, depression, catastrophizing and fear avoidance in those who responded to treatment. In future work, the use of all five questionnaires in one study may not be necessary and refinement of their role is required depending on the research question. This will be discussed further below.

As well as assessing the value of the questionnaires individually, it was important to look for correlations between the measures. With this in mind, it was of benefit to examine the associations between the worst pain score and the functional interference scores of the BPI. In addition, correlations were seen between the other questionnaires. It was also of interest to see that the BPI worst pain score and functional interference score, the FAPS and the PCS all correlated with aspects of gait as measured by the GAITRite. The FAPS questionnaire also correlated with the activity meter results.

Thus, associations were identified between the multi-dimensional components of CIBP: pain, sensation, mood and function. It is appreciated that this is not indicative of causality, but it is important to document for a number of reasons. Firstly, if certain issues, such as psychological distress, are not identified, then they remain untreated, with a potentially detrimental effect on quality of life. This may be due to patient reluctance to report these types of problems or clinicians not asking the right questions, but considering the other factors associated with CIBP may allow earlier intervention to improve patient outcomes. In addition, by treating one symptom, other symptoms may also improve. One suggestion is the use of "cross-over" interventions (312, 313). The theory is that established treatment for one symptom may cross-over and reduce the burden of another. Fleishman uses the symptoms of pain, fatigue and depression as possible targets for this type of intervention. Examples include nutritional therapies for pain and depression, exercise for depression and fatigue, medications for depression and fatigue and cognitive-behavioural therapies for pain (312). If symptoms occurring in association have the same aetiology, underlying biology or the same treatment is indicated for more than one symptom, then choosing one treatment for multiple symptoms has potential advantages. As well as improving or relieving more than one symptom, additional benefits include reducing the risk of treatment-related side effects and economic gains (314). Cleeland et al. addressed whether there is a underlying biological basis for symptoms occurring in association or clusters (315). The suggestion is that cytokines may play a mechanistic role in cancer-related symptoms, and therefore may be a potential target for novel treatments.

10.3.2 Value of GAITRite and activPAL to Assess Function in CIBP

At the first assessment, all patients completed an assessment of gait using the GAITRite electronic walkway. This was a very simple method for patients with which to measure function. As previously stated, the only disadvantage was the time taken to set it up beforehand for the clinician prior to patient arrival. However, this could be improved with future use by having a dedicated area for the walkway to be permanently set up. Although no control data were collected from a healthy population, comparison with the available literature showed that patients with CIBP walked much more slowly. After XRT, gait improved with increased velocity and cadence, but the differences were small and not statistically significant. In addition, no difference was seen depending on response to XRT. All but one patient were able to use the activity meters to measure general activity prior to XRT. When this data was compared to readings from healthy volunteers it demonstrated that patients with CIBP were a statistically significantly frailer, less active population. In a similar manner to the gait assessment, no significant difference was seen with the activity meters after XRT in the group as a whole, responders or non-responders.

Use of both the GAITRite and activPAL to measure function were novel in this population, but were user friendly and appeared acceptable to patients. It was felt to be important to measure function objectively in this study and the measures were successful in this regard. The evidence for use of objective functional assessments in the literature is scant and as such further work in this area is crucial. However, they were less helpful in assessing response to treatment, but as previously discussed this may have been due to a variety of reasons. Improvement in pain after XRT may not result in functional benefit for patients, changes may have been too small to be measured by the instruments chosen, the tools may have been inappropriate to use, or patient numbers may have been inadequate. In addition, confounding factors play a large role.

Despite not demonstrating any differences in function after treatment in patients with CIBP, the activPAL did have potential utility in helping to predict which patients were able to complete a follow up assessment. Statistically significant differences were seen between those who completed two assessments and those who dropped out. The latter were a less active group at baseline, spending fewer hours standing and stepping, taking fewer steps and using less energy. Energy expenditure was independently predictive in the multivariate analysis. Thus, when attrition rates are potentially high, and it would be of benefit to be able to gauge fitness to participate in a study or suitability for a particular treatment, a predictive measure would be of value. Therefore, with this in mind, a measure of function such as the activPAL may have clinical utility in the future.

10.4 Clinical Biomarker Development

The final aim of the current work was to explore whether clinical biomarkers can be developed to aid in the prediction of response to treatment, focusing on XRT for CIBP. It was clear from reviewing the literature that very little work has been done in this field. XRT research has primarily examined optimal dose and fractionation. In addition, to try to improve comparability of trials in pain research the International Bone Metastases Consensus Working Party recommended a set of criteria and endpoints (114, 115). In the current work, multivariate analysis was performed to assess the presence of potential biomarkers. Although associations were seen between analgesic response and psychological factors, none of the questionnaires or functional assessment tools provided independently predictive measures. However, using sensory testing, it was seen that patients with altered cool sensitivity (either increased or reduced) at the site of bone pain prior to XRT was predictive of response to treatment. Those with abnormal cool sensation had a better analgesic response to XRT for CIBP. This has not been demonstrated before and is an exciting finding in a relatively small study. However, it reflects what was seen in the pilot QST work suggesting that altered thermal processing may be mirroring the underlying plasticity of the spinal cord. QST has been used in other areas of pain research, such as diabetic neuropathy, to look to predictive factors, but its use in cancer pain appears novel in this regard. Therefore, the study provides a good basis for developing this theory further to see whether it can be utilised in everyday clinical practice. Being able to provide individualised treatment potentially has both personal and health economic rewards.

Patients have also been informed of the study outcomes. The letter is included in the Appendix.

10.5 Future Research

Now this study has finished, it is important to disseminate the salient findings and to consider further studies to substantiate the results. With this in mind, the next priority is to publish the work in high impact Oncology and Palliative Medicine journals and to present the study at national and international conferences. Two abstracts have been accepted for poster presentation at the 6th Research Congress of the EAPC in 2010 (see Appendix). In addition, a third abstract has been accepted for poster presentation at the 2010 American Society of Clinical Oncology Annual Meeting in Chicago (see Appendix).

The main finding that warrants further research is the suggestion that abnormal cool sensation is predictive of analgesic response to XRT. To take this forward, a larger prospective multi-centre observational study design would be optimal. Patients with CIBP undergoing XRT with the same inclusion and exclusion criteria as the study described in Chapter 6 would be appropriate. It would also seem advisable to complete a baseline assessment prior to XRT and a further assessment 6-8 weeks after XRT, as it is appreciated now that this is the best time to assess response to treatment. The definition of response to treatment should be similar to that described in Chapter 8, with a responder requiring a reduction in worst pain score of $\geq 30\%$ after treatment. However, to increase the comparability with other research and to increase the quality of the trial findings, it would be sensible on this occasion to include analgesic requirements in the definition of response as guided by the International Bone Metastases Consensus Working Party (115). Using measurement of worst pain score on a patient-assessed ordinal scale of 0-10 is also one of the agreed criteria suggested by the organisation. Therefore, using the short form BPI would be appropriate as one the study assessments. For this work, it would not be necessary to include the other four questionnaires. Although, they were of value to characterise CIBP, they are not vital in a study with the specific aim of confirming presence of biomarkers of response to XRT. However, has discussed previously, it is often of value to have a measure of quality of life in modern research. It may therefore be worth considering the use of the new EORTC QLQ-BM22 which tackles functional interference and psychological aspects of CIBP in one questionnaire specifically designed for patients with bone metastases. However, care must be taken in further research to have a specific research question with fewer parameters. In the current work it was necessary to have numerous variables to encompass the multi-dimensional components of CIBP, but it can be heavily criticised when multiple endpoints are analysed statistically. Reduction in the number of tools used will also encourage more centres to participate.

Therefore, in conjunction with the BPI (+/- the BM22), the only other assessment tool in the next study should be QST. This can also be more focussed. It was clear from the current study that use of the von Frey filaments to measure MDT and MPT, and calculation of the wind up ratio were not of value in this setting, and hence they should not be included. Brush and pin prick stimuli were of interest, but because thermal sensation consistently appeared to be the most indicative, it should be the priority. It would also seem sensible to refine the thermal QST tools. In the current work, just two temperatures were used and this allowed the assessment of warm and cool hyperaesthesia, hypoaesthesia and allodynia to thermal stimulus. However, this did not allow the measurement of thermal thresholds. It would be useful to assess this in the next study by examining a range of temperatures in patients with CIBP. Although, VAS overall was not found to be of major benefit when used to measure the pain intensity of certain stimuli, there was a significant difference compared with the control site for cool sensation. Therefore, it would still be prudent to measure pain intensity with thermal testing, but the NRS would be preferable to the VAS for the reasons already discussed. In the future, it may also be worth considering carrying out a QST assessment earlier after XRT to assess possible early sensory changes as well as at 6-8 weeks. This may allow assessment of how quickly the sensory changes occur which may reflects the processes of reduced inflammation or tumour death.

A number of other issues would need consideration in future trials. The first relates to study size. Although statistical advice was sought with regards to the current work, it is appreciated that the study sample was small. Therefore, further work should aim to recruit much larger numbers of patients as directed by an appropriate power calculation. Another consideration is the members of the team involved in the next study. It was of benefit to have one person carrying out the QST to improve consistency and reduce inter-rater variability. However, it relies on the integrity of the researcher to report the true findings and is open to potential exploitation and the Hawthorne effect. In addition, in the current work, when the author was not in the department, for example for annual leave or conferences, no study assessments were done during this time. This restricts potential recruitment and having a research team comprising a number of medical and nursing staff who are trained fully in the study procedures would be advantageous. Above all the results need to be valid, reproducible and reliable and it is a balance between these factors to achieve the optimal outcome.

10.6 Conclusion

In the work described in this thesis, using a clearly defined combination of assessments enabled patients with painful bony metastases to have their pain characterised and a potential clinical biomarker of response to XRT was discovered. For everyday clinical practice, it is necessary to have outcome measures that are practical enough to be easily used in all patients and comprehensive enough to be useful in evaluation of patients with pain (167). Therefore, future research needs to take this into account to allow a management approach with high clinical return.

Chapter 11 CONCLUSIONS & RECOMMENDATIONS

11.1 Conclusions

From reviewing the literature we know that CIBP is a major clinical problem. Breast, prostate and lung cancer are common with a high probability of developing symptomatic bony metastases. With improving anti-cancer therapies and an aging population, more patients are living longer with cancer and bony disease. Patients with CIBP have increased morbidity, reduced performance, disruption of mood and poor quality of life. The gold standard treatment for CIBP is XRT. In addition, analgesics, adjuvants, bisphosphonates, radioisotopes, chemotherapy and hormonal therapy are available components of the armamentarium for CIBP. Alternative or complementary techniques include surgical, radiological or anaesthetic intervention. Despite this, pain control for CIBP remains suboptimal. Exploring CIBP in animal models has aided advancement of the management of CIBP in patients. Review of the anatomy and physiology of bone, the mechanisms of bone metastases and pain pathways has helped to increase understanding of the underlying mechanisms of CIBP. Unfortunately the full picture is not completely clear, but it does seem that CIBP is a unique pain syndrome. To explore this further, the work presented in this thesis aimed to examine sensory processing in patients with CIBP. From the literature review, it was clear that pain is associated with mood and function. It was also evident that a comprehensive technique to assess CIBP, which takes into account the mutidimensional components of the pain syndrome, was not available. Therefore, this research aimed to develop a method of assessment to characterise CIBP fully, to measure response to treatment and to look for potential clinical biomarkers of response to treatment. The main findings are highlighted below.

11.1.1 Clinical Characterisation of CIBP

An assessment of CIBP characterising the cognitive, affective, sensory and functional components of CIBP was clinically practical and highly acceptable to patients. The demographic of the population studied was representative of patients with CIBP in comparison with published data, but despite being a heavily pre-treated population using a combination of analgesics, pain was severe in nature. Variation in pain intensity and the presence of breakthrough pain confirmed the importance of measuring worst pain in patients with CIBP. This is of paramount importance and is clinically useful when considering treatment options for patients. The research also demonstrated clear evidence of relationships between CIBP and anxiety, depression, fear avoidance and catastrophizing. Although levels of these were surprising low, a third of patients were classified as having clinically significant emotional distress. It may not be easy in a busy clinical environment to address these important issues, especially if knowledge and understanding of the psychological aspects of pain are limited. However, exploring these subjects may be highly valuable for patients, especially if life expectancy is poor. If areas of concern are raised, alternative strategies may be available (in conjunction with members of a multi-disciplinary team), to reduce distress in this population, with the aim of improving quality of life. Clinicians may also be more inclined to treat a specific problem, if treatment of one symptom may potentially reduce the severity of other associated symptoms.

A relationship was also seen between CIBP and function. Using objective measures of function, patients with CIBP were a frailer, less active population compared with healthy adults. Whatever the level of function, whether this is simply being able to carry out activities of daily living independently or being able to continue with more energetic premorbid activities, patients confirm that this is a key element to address.

Clear evidence of altered sensory processing was seen at the site of CIBP with abnormalities in both mechanical and thermal QST parameters. This has not been demonstrated previously and is an exciting clinical insight into the underlying mechanisms. Increasing knowledge of the pathophysiology may aid the development of novel therapies for CIBP.

11.1.2 Effect of XRT on CIBP

Seventy percent of patients in the study were able to complete a follow up assessment 6-8 weeks after treatment. Overall, CIBP significantly improved with XRT in these patients, with statistically significant reductions in worst, least, and average pain scores and functional interference as measured by the BPI. It was encouraging to see that mood, fear avoidance and catastrophizing also improved significantly after XRT, with fewer patients classified as being clinically significantly emotionally distressed. However, it was crucial to explore this further to see whether these changes mirrored the analgesic response to treatment.

Marked QST changes were seen in response to XRT, but to determine the clinical utility, as with the psychological parameters, required further investigation. It was fundamental to determine whether the sensory differences varied between those with a response to treatment and those who did not benefit from XRT for CIBP.

No statistically significant differences in objective measures of function were seen after XRT, but those patients who dropped out prior to follow up were significantly frailer as measured with activity meters and performance status. In addition, they had higher levels of depression and fear avoidance behaviour. It may be difficult to appreciate a patient's functional status when seeing only a snapshot of their performance when attending a clinic, for example. Therefore, having an objective measure of function may be clinically useful to aid decision making when considering fitness for treatment or inclusion in clinical trials.

11.1.3 Characteristics of Patients with a Clinically Significant Analgesic Response to XRT

Twenty-nine patients (69% evaluable, 48% intention-to-treat) achieved an analgesic response to XRT for CIBP, as defined as an improvement of $\geq$ 30% in worst BPI score two months after treatment. Trends were seen in the demographics of those who responded to treatment and non-responders. Proportionally more responders were male with prostate cancer and in a relationship. In responders, performance status improved and fewer required additional chemotherapy or analgesia, although the morphine requirements between the two groups did not differ significantly. All dimensions of pain (as measured with the BPI and MPQ), anxiety, depression, fear avoidance and catastrophizing significantly improved in responders, but not in non-responders. This does not provide evidence of a causal relationship, but it is of significant clinical benefit. By treating pain, it is hopeful for patients that other aspects of the pain experience may improve in parallel. In particular, in those patients who do not gain analgesic benefit from XRT, it would be prudent to ensure their psychological needs are met appropriately, in conjunction with addressing their ongoing pain.

Despite the fact that no objective functional differences were seen after XRT between responders and non-responders, it was still of benefit to explore the applicability of using tools such as the GAITRite walkway and activPAL in patients with CIBP. Their ease of use and acceptability mean that they may have value in another research setting.

Overall, XRT did result in alterations in response to evoked stimuli in responders, with a greater number of patients in whom sensation normalised after XRT compared with non-responders. Patients with a combination of altered sensation to thermal, pin prick and wind up stimuli showed the largest reduction in worst pain score after XRT. In addition, **abnormal cool sensation was an independent predictor of analgesic response to XRT for CIBP**. This exciting finding is highly clinically relevant, as assessment of thermal sensitivity could be incorporated easily into routine practice to aid decisions on management for patients with bone pain.

11.2 Recommendations

Patients with bony metastases have pain which impacts on their physical and emotional well-being with relationships between pain, mood, fear avoidance, catastrophizing, level of function and sensory processing. Therefore, it is vital that these important components of CIBP are assessed in a comprehensive, but patient-friendly manner to allow early identification and treatment of pain and its associated problems. Although acceptable to patients as part of a clinical trial, it is appreciated that the full array of questionnaires and tools used in this research would not be practical in routine clinical practice. However, by completing a very detailed evaluation of CIBP in a research setting, we can direct a manageable assessment of probable "high return" in the clinic. For example, when reviewing patients with CIBP, a simple, key aim would be to elicit the worst pain score. It would also be feasible to test for thermal abnormalities. This needs further work to refine the paradigm in a larger clinical trial, but seems to be an important step towards clinical biomarker development in this setting. It may also then prove useful to consider its use in assessing other chronic pain syndromes and their response to treatment. In conjunction with this, ongoing translational work in animal models, with collaboration between scientists and clinicians is vital to promote ideas and potential new therapies from bench to bedside to optimise targeted treatment for patients.

Chapter 12 GLOSSARY OF ABBREVIATIONS

ACS	Angela Clare Scott
ADLs	Activities of Daily Living
AMPA	α-Amino-3-Hydroxy-5-methyl-4-Isoxazole Propionic Acid
ASIC	Acid Sensing Ion Channels
ATC	Around The Clock
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
BTP	Breakthrough Pain
BTPQ	Breakthrough Pain Questionnaire
CAMs	Cell Adhesion Molecules
CCK	Cholecystokinin
CCR	Chemotactic Cytokine Receptor
CES-D	Centre for Epidemiological Studies Depression Scale
CFA	Complete Freund's Adjuvant
CGRP	Calcitonin Gene Related Peptide
CI	Confidence Interval
CIBP	Cancer-Induced Bone Pain
Cm	Centimeter
CNS	Central Nervous System
COX	Cyclo-oxygenase
CRP	C-Reactive Protein
CT	Computed Tomography
DFNS	German Research Network on Neuropathic Pain
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAPC	European Association for Palliative Care
EAS	Effective Analgesic Score
ECOG	Eastern Cooperative Oncology Group
EDS	Edinburgh Depression Scale
EORTC	European Organisation for Research and Treatment of Cancer
EPDS	Edinburgh Postnatal Depression Scale

ESAS	Edmonton Symptom Assessment Scale
FABQ	Fear Avoidance Beliefs Questionnaire
FP	Functional Ambulation Performance
FAPS	Fear and Avoidance of Pain Scale
FDG	Fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
FPQ	Fear of Pain Questionnaire
GABA	γ-Aminobutyric Acid
GC	Gate Cycle
GCP	Good Clinical Practice
GCT	Gate Control Theory
GFAP	Glial Fibrillary Acidic Protein
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
5-HT	5-Hydroxytryptamine (Serotonin)
^{131}I	Radioiodine
IASP	International Association for the Study of Pain
ICH	International Committee for Harmonisation
IFN	Interferon
IGF	Insulin-like Growth Factor
IL	Interleukin
IMMPACT	Initiative on Methods, Measurement & Pain Assessment in Clinical Trials
IV	Intravenous
JNDs	Just Noticeable Differences
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LDH	Lactate Dehydrogenase
LT	Low Threshold
LTD	Long Term Depression
LTP	Long Term Potentiation
MCP	Monocyte Chemoattractant Protein
MDT	Mechanical Detection Threshold
MET	Metabolic Equivalent

MIAs	Mechanically Insensitive Afferents
Min	Minute
MPQ	McGill Pain Questionnaire
MPT	Mechanical Pain Threshold
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NGF	Nerve Growth Factor
NHS	National Health Service
NMDA	N-Methyl-D-Aspartate
NPY	Neuropeptide Y
NRS	Numerical Rating Scale
NS	Nociceptive Specific
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NTX	n-telopeptide of type 1 collagen
^{32}P	Radioactive Phosphorus
PCS	Pain Catastrophizing Scale
PDGF	Platelet Derived Growth Factor
PET	Positron Emission Tomography
POMS	Profile of Mood States
PPI	Present Pain Intensity
PRI	Pain Rating Index
PS	Performance Status
PSA	Prostate Specific Antigen
PTH-rP	Parathyroid Hormone Related Peptide
QLQ	Quality of Life Questionnaire
OPG	Osteoprotegerin
QST	Quantitative Sensory Testing
QSART	Quantitative Sudomotor Axon Reflux Testing
OTFC	Oral Transmucosal Fentanyl Citrate
RANK	Receptor Activator for Nuclear Factor κB
RANKL	Receptor Activator for Nuclear Factor κB Ligand
RCT	Randomised Controlled Trial

RTOG	Radiation Therapy Oncology Group
^{153}Sm	Samarium
^{89}Sr	Strontium
Sec	Second
SC	Subcutaneous
SF-MPQ	Short Form McGill Pain Questionnaire
SIGN	Scottish Intercollegiate Cancer Network
S-LANSS	Self-report Leeds Assessment of Neuropathic Symptoms and Signs
SNL	Spinal Nerve Ligation
SNS	Sympathetic Neurons
SP	Substance P
SPR	Substance P Receptor
SRE	Skeletal Related Event
SSRI	Selective Serotonin Reuptake Inhibitor
^{186}Re	Rhenium
TCA	Tricyclic Antidepressant
TENS	Transcutaneous Electrical Nerve Stimulation
TGF	Transforming Growth Factor
TMRC	Translational Medicine Research Collaboration
TNF	Tumour Necrosis Factor
TRP	Transient Receptor Potential (V1/V2/M8/A1)
USB	Universal Serial Bus
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VIP	Vasoactive Intestinal Peptide
VR1	Vanilloid Receptor 1
VRL-1	Vanilloid Receptor-Like Protein 1
VRS	Verbal Rating Scale
WDR	Wide Dynamic Range
WHO	World Health Organisation
WUR	Wind Up Ratio
XRT	Radiotherapy

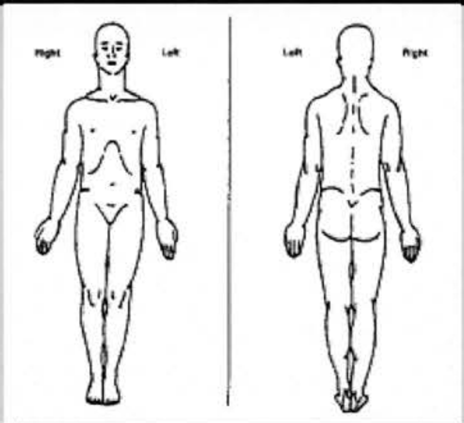
Chapter 13 APPENDICES

A. *Brief Pain Inventory (Short Form)*

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7.	What treatments or medications are you receiving for your pain?

8.	In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief	10%	20%	30%	40%	50%	60%	70%	80%	90%	100% Complete Relief

9.	Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

B. Mood

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

C. Walking Ability

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

E. Relations with other people

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

F. Sleep

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

B. *McGill Pain Questionnaire (Short Form)*

PATIENT'S NAME: ____________________ DATE: __________

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN |————————————————————| WORST POSSIBLE PAIN

PPI

0	NO PAIN	_____
1	MILD	_____
2	DISCOMFORTING	_____
3	DISTRESSING	_____
4	HORRIBLE	_____
5	EXCRUCIATING	_____

C. Hospital Anxiety and Depression Scale

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':		**A**	**I feel as if I am slowed down:**	**D**	
Most of the time		3	Nearly all of the time	3	
A lot of the time		2	Very often	2	
Time to time, occasionally		1	Sometimes	1	
Not at all		0	Not at all	0	
I still enjoy the things I used to enjoy:	**D**		**I get a sort of frightened feeling like 'butterflies in the stomach':**		**A**
Definitely as much	0		Not at all		0
Not quite so much	1		Occasionally		1
Only a little	2		Quite often		2
Not at all	3		Very often		3
I get a sort of frightened feeling like something awful is about to happen:		**A**	**I have lost interest in my appearance:**	**D**	
Very definitely and quite badly		3	Definitely	3	
Yes, but not too badly		2	I don't take as much care as I should	2	
A little, but it doesn't worry me		1	I may not take quite as much care	1	
Not at all		0	I take just as much care as ever	0	
I can laugh and see the funny side of things:	**D**		**I feel restless as if I have to be on the move:**		**A**
As much as I always could	0		Very much indeed		3
Not quite so much now	1		Quite a lot		2
Definitely not so much now	2		Not very much		1
Not at all	3		Not at all		0
Worrying thoughts go through my mind:		**A**	**I look forward with enjoyment to things:**	**D**	
A great deal of the time		3	A much as I ever did	0	
A lot of the time		2	Rather less than I used to	1	
From time to time but not too often		1	Definitely less than I used to	2	
Only occasionally		0	Hardly at all	3	
I feel cheerful:	**D**		**I get sudden feelings of panic:**		**A**
Not at all	3		Very often indeed		3
Not often	2		Quite often		2
Sometimes	1		Not very often		1
Most of the time	0		Not at all		0
I can sit at ease and feel relaxed:		**A**	**I can enjoy a good book or radio or TV programme:**	**D**	
Definitely		0	Often	0	
Usually		1	Sometimes	1	
Not often		2	Not often	2	
Not at all		3	Very seldom	3	

D. Fear and Avoidance of Pain Scale

Here are some statements about how pain can affect various activities. Next to each statement is a scale to mark your answer. Please circle the number that corresponds to how often each situation occurs. In the second section, please circle the number that corresponds to how strongly you agree or disagree with the statement.

	NEVER			HALF THE TIME		ALL THE TIME	
1. I avoid going out socially with my partner / family / friends as it increases my pain.	0	1	2	3	4	5	6
2. I avoid visiting friends or have them visit me as it increases my pain.	0	1	2	3	4	5	6
3. I travel in the car less as it increases my pain	0	1	2	3	4	5	6
4. I avoid heavy housework as it causes more pain	0	1	2	3	4	5	6
5. I do less shopping as it causes more pain	0	1	2	3	4	5	6
6. I cook less as it increases my pain	0	1	2	3	4	5	6
7. I avoid carrying as it increases my pain	0	1	2	3	4	5	6
8. I try not to do activities that increase my pain	0	1	2	3	4	5	6
9. I move slower to avoid an increase in pain	0	1	2	3	4	5	6
10. I move differently to avoid an increase in pain	0	1	2	3	4	5	6
11. I tend not to lift heavy objects as it increases my pain	0	1	2	3	4	5	6
12. I am cautious about bending as it causes more pain	0	1	2	3	4	5	6
13. I am cautious about stretching as it causes more pain	0	1	2	3	4	5	6
14. I avoid standing as it increases my pain	0	1	2	3	4	5	6
15. I walk less as it increases my pain	0	1	2	3	4	5	6
16. I avoid any exercise as it increases my pain	0	1	2	3	4	5	6
17. I lie down / rest more due to pain	0	1	2	3	4	5	6
18. I am unable to do my normal work as it increases my pain	0	1	2	3	4	5	6
19. I tend not to stay in one position too long as it increases my pain	0	1	2	3	4	5	6
	STRONGLY DISAGREE			UNSURE		STRONGLY AGREE	
20. I should not do activities that increase my pain	0	1	2	3	4	5	6
21. Activities that cause more pain might be harmful	0	1	2	3	4	5	6

E. Pain Catastrophizing Scale

Please think about painful experiences you have had recently. Below are some statements about how pain can affect your thoughts and feelings. Next to each statement is a scale to mark your answer. Read each item and place a firm tick in the box opposite the reply that comes closest to how often each situation occurs.

	Not at all		Half the time		All the time
	0	1	2	3	4
1. I worry all the time about whether the pain will end.					
2. I feel I can't go on.					
3. It's terrible and I think it's never going to get any better.					
4. It's awful and I feel that it overwhelms me.					
5. I feel I can't stand it any more.					
6. I become afraid that the pain may get worse.					
7. I think of other painful experiences.					
8. I anxiously want the pain to go away.					
9. I can't seem to keep it out of my mind.					
10. I keep thinking about how much it hurts.					
11. I keep thinking about how badly I want the pain to stop.					
12. There is nothing I can do to reduce the intensity of the pain.					
13. I wonder whether something serious may happen.					

F. *Ethical Approval for Pilot Study 1 & 2*

LOTHIAN RESEARCH ETHICS COMMITTEE

CERTIFICATE OF ETHICAL OPINION

LREC Reference Number: LREC/2003/8/11
Title: Characterisation of the Physical Properties of the Pain Caused by Bone Malignancy and Comparison with the Physical Properties of Neuropathic Pain.
Researcher: Dr John Walley

The Medicine/Clinical Oncology II Research Ethics Committee of the Lothian Research Ethics Committee (the Committee) reviewed this proposed research and is of the opinion that it is ethical and appropriate to be carried out in the Lothian Area. This opinion encompasses all aspects of the application including the Patient/Subject Information Sheet and all other accompanying documentation provided.

The LREC application form, protocol, subject information sheet, information on compensation arrangements, payments to researchers and the provision of expenses to subjects (where appropriate) were reviewed and approved and the members of the Committee present at the meeting are shown on the attached *Membership List*.

This opinion is issued subject to the following conditions and is invalid if they are not followed:

- You must obtain appropriate management approval from the relevant NHS Trust(s) before starting the proposed research. It is the NHS Trust(s) that ultimately decide whether or not this research should go ahead taking account of the advice of the Local Research Ethics Committee.
- You must notify the Sub-Committee and the relevant NHS Trust(s), in advance, of any significant proposed deviation from the original protocol or application form and obtain approval for any such amendments using the *Amendment Approval Request Form.*
- You must submit reports to the Sub-Committee and the NHS Trust(s) once the study is underway if there are any unusual or unexpected results which raise questions about the safety of the research.
- You must report annually on successes, or difficulties, in recruiting subjects in order to provide useful feedback on perceptions of the study among patients and volunteers using the *Progress Report Form.*
- Where the study is terminated prematurely you must report within fifteen days indicating the reasons for early termination.
- You must submit a final report within three months of the completion of the study using the *Progress Report Form.*

Peter Reith
Secretary
Lothian Research Ethics Committee

21 March 2003

Joyce Clearie
Administrator
Medicine/Clinical Oncology II
Research Ethics Committee

G. *R&D Approval for Pilot Study 1 & 2*

The Lothian University Hospitals NHS Trust

ROYAL INFIRMARY OF EDINBURGH
51 Little France Crescent, Edinburgh, EH16 4SA

NHS

Lothian

RESEARCH & DEVELOPMENT OFFICE

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FRCPath

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Administrative Assistant:
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Alison Clark
RGN BSc (Hons)

HAC/GO/app1c/patnoncomm

26 March 2003

Dr J Walley
Research Fellow in Palliative Care
Clinical Oncology
Western General Hospital
Crewe Road

Dear Dr Walley

LREC No:	**2003/8/11**
R&D Project ID No:	**2002/W/ON/29**
Title of Research	*Characterisation of the physical properties of the pain caused by bone malignancy and comparison with the physical properties of neuropathic pain*

The above project has undergone a review of resource and financial implications by the R&D Office and I am satisfied that all the necessary arrangements have been set in place.

On behalf of the Trust Chief Executive and Medical Director, I am happy to give Trust management approval to allow the project to commence, subject to the approval of the appropriate Research Ethics Sub-Committee having also been obtained. **It is a condition of this management approval that your Clinical Director gives his/her agreement for the project to be undertaken. Please ensure that the enclosed costing sheet is signed and returned to the R&D Office as quickly as possible.**

We would ask you to note that under Section 7, question 34, The Lothian University Hospitals NHS Trust provides indemnity for negligence for NHS and honorary clinical staff wherever research involves patients attending the hospitals. It is not empowered to provide non negligent indemnity for patients or volunteers.

Yours sincerely

Dr Heather A Cubie
R&D Director

~~**enc — R&D approval sheet**~~

cc *Secretary, Research Ethics Sub-Committee*

H. *Patient Information Sheet for Pilot Study 1*

Patient Information Sheet (version 1)

NHS
Lothian

Study Title

Characterisation of the pain produced by bone malignancy and comparison with a characterisation of neuropathic pain.

Explanation of the Title
This project aims to study how people describe their pain. We are especially interested in people with pain caused by cancer in the bones and those who have nerve pain.

Introduction
Thank you for taking the time to read this. You are being asked to take part in this study because you have either bone pain caused by cancer or nerve pain. Your pain may be due to a problem you have at the moment or left over after treatment of a problem you had in the past. If you are concerned about your pain or what's causing it, please ask the study doctor or nurse to explain things further.

Before you decide to take part, please read this information sheet carefully. Ask us to explain anything that is not clear and please ask us if you would like more information about any part of the study.

*You are **not** obligued to take part in this study; it is your choice whether you take part or not. If you do take part you may change you mind and leave the study **at any time**. Leaving the study or not taking part will have **no** effect on your usual medical care and you will continue to be treated by your doctor(s) as before.*

Consumers for Ethics in Research (CERES) publish a leaflet entitled "Medical Research and You". This leaflet gives more information about medical research and looks at some questions potential recruits may want to ask. You may obtain copies from us or by writing to CERES, PO Box 1365, London, N16 0BW.

Why is this study being done?
The way people describe their pain can help doctors and nurses work out what is causing it. When we know what is causing a pain, we can treat it more effectively. In this study we are interested in people with pain caused by cancer in the bones. By knowing how people describe these pains, we hope to be able to speed up the diagnosis of bone cancer. We can then give them treatments like radiotherapy to help relieve the pain it can cause.

We are also hoping to compare how people describe bone pain to how people describe nerve pain. To do this we are asking people with nerve pain and bone pain to describe their pains to us.

If you want to know more about why this study is being done, make sure you ask the study doctor or nurse.

What the study involves for you

The study involves answering questions about your pain. You will be asked to fill in a questionnaire with the study doctor or nurse. These questions will include such things as how severe your pain is and which words you would use to describe it. The interview will last for about 30 minutes.

We will then ask some people if they would be willing to have some further tests performed on them. These are simple tests measuring the sensation in the skin at the site of peoples' pain. They will take a further 10 minutes to complete. They include very briefly pressing fine plastic fibres and warm and cool metal rollers against your skin. Most of the tests are not uncomfortable. **Two of the tests may produce very mild discomfort**, but this shouldn't last for more than a few seconds.

If you would be happy to answer the questionnaire, but not to take part in the sensory testing, please let the study doctor or nurse know.

Once you have completed the questionnaire and, if you are one of the patients selected to have them, the sensory tests, your involvement in the study will have finished.

Where and when will the study take place

If you agree to take part in the study, we will arrange a time to fill in the questionnaire with you. If you are happy to be interviewed today, we will take you to a private room and ask you about your pain. If you would like to take part, but would not want to do so today, then we will arrange a time to see you at the Western General Hospital or at your own home if you would prefer.

It is important that you have sufficient time to consider taking part in this study and that the study causes you as little inconvenience as possible. Some people may be happy to take part on the day they are first seen by the study team, whilst others will need longer to think about taking part. Please take as long as you wish before you decide whether to take part or not.

If you wish to be seen at the Western General Hospital, we will arrange for a taxi to gring you to the hospital. If this is for the sole purpose of this study, we will pay for this journey.

Consent to the study

If you do decide to take part you will be asked to sign a consent form, agreeing to the provisions of this information sheet. You will then be given a copy of the signed consent form. Your own hospital doctors and nurses are fully aware of the study and would be happy for you to take part if you wish to do so.

Before signing the form agreeing to take part, make sure that you are happy that you know what it involves for you.

Patient confidentiality
Any information that you give before or during the study will be kept in strict confidence. Your medical records may be read by the study doctor or nurse, but care will be taken so that you cannot be identified when we write reports of the study. Your full name will not be used on study documents; you will be referred to only by an identity number.

We will contact your GP to tell them about you taking part in the study. We will also tell them and your hospital doctors if you have pain that would require changes in your treatment.

Occasionally research projects are checked by regulatory authorities to ensure that research is being done properly. In this situation, these authorities may need to look at your medical notes.

The possible benefits to you
The study will provide a detailed assessment of your pain. If we discovered that your pain is troublesome, we will inform your own doctors so that changes can be made in your medication to improve your pain control.

The information you provide may help us diagnose bone pain more quickly and so help others be treated more effectively.

Who has reviewed the study?
This study has been looked at by a group of doctors, nurses and non-medical people whose job is to check that any research that is being done is both valuable and safe.

Who can I contact for further information?
If you would like any further information about this study you are welcome to contact either:
Dr John Walley*, Specialist Registrar with the Palliative Care Team at the Western General Hospital (tel 0131 537 100 or 0131 537 3114)
Or
Dr Marie Fallon, Consultant in Palliative Medicine at the Western General Hospital (tel 0131 537 1000)

If you would like to speak with someone who is independent of this study, please contact:
Dr Melanie Mackean, Consultant Oncologist at the Western General Hospital
(tel 0131 537 1000)

Thank you for taking the time to read this information sheet. We hope that you do decide to take part in the study, but reassure you that your care will not be affected in any way if you decide not to take part.

(* Data was collected by Siobhan Duncan in collaboration with Dr John Walley)

I. Consent Form for Pilot Study 1

Patient Identification Number for this trial: Date: NHS Lothian

CONSENT FORM Version 1

Title of Project:

Characterisation of the pain produced by bone malignancy and comparison with a characterisation of neuropathic pain.

Name of researchers:
Dr. John Walley, Specialist Registrar in Palliative Medicine
Dr. Marie Fallon, Consultant in Palliative Medicine

1. I confirm that I have read and understand the Patient Information Sheet dated ___/___/___ for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the interview section of the study.

5. I agree / do not agree (delete as appropriate) to have sensory testing performed on me as part of the above study, if I am asked to do so.

Name of Patient	Date	Signature
Name of Person Taking Consent (Researcher)	Date	Signature

One for patient, one for researcher & one to be kept with hospital notes

J. Patient Information Sheet for Pilot Study 2

Patient Information Sheet (version 3)

NHS
Lothian

Study Title

Characterisation of the physical properties of the pain caused by bone malignancy and comparison with the physical properties of neuropathic pain.

Explanation of the Title
This project aims to study how people describe their pain and how sensation is altered in areas affected by pain. We would also like to know how this is affected by treatment. We are especially interested in people with pain caused by cancer in the bones.

Introduction
Thank you for taking the time to read this. You are being asked to take part in this study because you have bone pain caused by cancer. Your pain may be due to a problem you have at the moment or left over after treatment of a problem you had in the past. If you are concerned about your pain or what's causing it, please ask the study doctor or nurse to explain things further. Before you decide to take part, please read this information sheet carefully. Ask us to explain anything that is not clear and please ask us if you would like more information about any part of the study.

*You are **not** obligued to take part in this study; it is your choice whether you take part or not. If you do take part you may change you mind and leave the study **at any time**. Leaving the study or not taking part will have **no** effect on your usual medical care and you will continue to be treated by your doctor(s) as before.*

Consumers for Ethics in Research (CERES) publish a leaflet entitled "Medical Research and You". This leaflet gives more information about medical research and looks at some questions potential recruits may want to ask. You may obtain copies from us or by writing to CERES, PO Box 1365, London, N16 0BW.

Why is this study being done?
The way people experience their pain can help doctors and nurses work out what is causing it. When we know what is causing a pain, we can treat it more effectively.

In this study we are interested in people with pain caused by cancer in the bones. By comparing sensation in the skin at the site of your pain with an unaffected area, we hope to be able to improve our understanding of the changes which occur when people experience pain due to cancer in the bones. We can then understand how treatments like radiotherapy help to relieve pain and have a basis for the development of new ways to relieve pain.

If you want to know more about why this study is being done, make sure you ask the study doctor or nurse.

What the study involves for you

The study involves answering questions about your pain. These questions will include such things as how severe your pain is and how you would describe it. This should take 10-15 minutes. We will then perform some simple tests measuring the sensation in the skin at the site of your pain and at an unaffected area for comparison. This will take about 20-30 minutes to complete. The tests include very briefly pressing fine plastic fibres and warm and cold rollers against your skin. Most of the tests are not uncomfortable. **Two of the tests may produce very mild discomfort**, but this should not last for more than a few seconds.

After you have had radiotherapy for your pain we will repeat the assessment. This will happen about 4-6 weeks later, at a time that suits you. Once you have completed this repeat assessment, your involvement in the study will have finished.

If you have private medical insurance you should check with the company before agreeing to take part in the trial. You will need to do this to ensure that your participation will not affect your medical insurance.

Where and when will the study take place

If you agree to take part in the study, we will arrange a time for you to be asked the questions and have the sensory tests carried out. If you are happy to do this today, we will take you to a private room to do so. If you would like to take part, but would not want to do so today, then we will arrange a time to see you at the Western General Hospital or at your own home if you would prefer.

It is important that you have sufficient time to consider taking part in this study and that the study causes you as little inconvenience as possible. Some people may be happy to take part on the day they are first seen by the team, whilst others will need longer to think about taking part. Please take as long as you wish before you decide to take part or not.

Consent to the study

If you do decide to take part, you will be asked to sign a consent form, agreeing to the provisions of this information sheet. You will then be given a copy of the signed consent form. Your own hospital doctors and nurses are fully aware of the study and would be happy for you to take part if you wish to do so.

Before signing the form agreeing to take part, make sure that you are happy that you know what it involves for you.

Patient confidentiality

Any information that you give before or during the study will be kept in strict confidence. Your medical records may be read by the study doctor or nurse, but care will be taken so that you cannot be identified when we write reports of the study. Your full name will not be used on study documents. Here you will be referred to only by an identity number.

We will contact your own GP to tell them about you taking part in the study. We will also tell them and your hospital doctors if you have pain that would require changes in your treatment. Should there be any significant findings during the study, then we will inform you and your doctors of these.

Occasionally research projects are checked by regulatory authorities to ensure that the research is being done properly. In this situation, these authorities may need to look at your medical notes.

The possible benefits to you
The study will provide a detailed assessment of your pain. If we discovered that your pain is troublesome, we will inform your own doctors so that changes can be made in your medication to improve your pain control.

The information you provide may help us diagnose bone pain more quickly and better understand the changes which occur when cancer affects bone. It may also help others to be treated more effectively.

Who has reviewed the study?
This study has been looked at by a group of doctors, nurses and non-medical people whose job is to check that any research that is being done is both valuable and safe.

Who can I contact for further information?
If you would like any further information about this study you are welcome to contact either:
Dr Sandra McConnell, Specialist Registrar in Palliative Care, Western General Hospital (tel 0131 537 3114)
Or
Dr Marie Fallon, Consultant in Palliative Medicine, Western General Hospital
(tel 0131 537 1000)

If you would like to speak with someone who is independent of this study, please contact:
Dr Melanie Mackean, Consultant Oncologist, Western General Hospital
(tel 0131 537 1000)

Thank you for taking the time to read this information sheet. We hope that you do decide to take part in the study, but we reassure you that your care will not be affected in any way if you decide not to take part.

K. Consent Form for Pilot Study 2

Patient Identification Number for this trial: Date:

NHS Lothian

CONSENT FORM Version 2

Title of Project:

Characterisation of the pain produced by bone malignancy and comparison with a characterisation of neuropathic pain by quantitative sensory testing.

Name of researchers:
Dr. Sandra McConnell, Specialist Registrar in Palliative Medicine
Dr. Marie Fallon, Consultant in Palliative Medicine

1. I confirm that I have read and understand the Patient Information Sheet dated ___/___/___ for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study.

Name of Patient	Date	Signature
Name of Person Taking Consent (Researcher)	Date	Signature

One for patient, one for researcher & one to be kept with hospital notes

L. *Ethical Approval for Main Study*

Lothian NHS Board

Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
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www.nhslothian.scot.nhs.uk

NHS
Lothian

23 JUL 2007

Lothian Local Research Ethics Committee 02
Telephone: 0131 536 9061
Facsimile: 0131 536 9346

19 July 2007

Professor Marie Fallon
Honorary Consultant in Palliative Medicine
University of Edinburgh
Edinburgh Cancer Centre,
School of Molecular and Clinical Medicine,
Western General Hospital, Edinburgh
EH4 2XU

Dear Professor Fallon

Full title of study: **Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain.**
REC reference number: **07/S1102/27**

Thank you for your letter of 22 June 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Sub-Committee of the REC held on 10 July 2007.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	1	18 May 2007
Investigator CV		15 May 2007
Protocol	1	16 May 2007
Covering Letter		16 May 2007
Summary/Synopsis	1	16 May 2007
Questionnaire: Pain Catastrophizing Scale	Validated	

INVESTOR IN PEOPLE

Questionnaire: Fear and Avoidance of Pain Scale	Validated	
Questionnaire: HAD Scale	Validated	
Questionnaire: Short-Form McGill Pain Questionnaire	Validated	
Questionnaire: Brief Brain Inventory (short form)	Validated	
GP/Consultant Information Sheets	1	11 May 2007
Participant Information Sheet: Participants	1	11 May 2007
Participant Information Sheet: Participant	2	21 June 2007
Participant Consent Form: Participants	1	11 May 2007
Response to Request for Further Information		22 June 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/S1102/27	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Professor Peter Hayes
Chair

Email: lyndsay.baird@lhb.scot.nhs.uk

Copy to: Mrs Marise Bucukoglu, University of Edinburgh

Lothian Local Research Ethics Committee 02

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/S1102/27	**Issue number:**	0	**Date of issue:**	19 July 2007
Chief Investigator:	Professor Marie Fallon				
Full title of study:	Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain.				

This study was given a favourable ethical opinion by Lothian Local Research Ethics Committee 02 on 10 July 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes [1]*
Professor Marie Fallon	Honorary Consultant in Palliative Medicine	NHS Lothian	Lothian Local Research Ethics Committee 02	19/07/2007	

Approved by the Chair on behalf of the REC:

.... (Signature of ~~Chair~~/Co-ordinator)
(delete as applicable)

.... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

M. R&D Approval for Main Study

University Hospitals Division

Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

NHS Lothian

RESEARCH & DEVELOPMENT OFFICE
Room E1.12

Tel: 0131 242 3330
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Director:
Professor Heather A Cubie

R&D Governance Manager:
Dr Tina McLelland

PA to Professor Cubie & Dr McLelland:
Mrs Jill Kelly

Commercial Research Manager:
Dr Douglas Young

Research Manager Capacity & Capability:
Dr Janet Hanley

Research Governance Co-ordinator:
Mrs Susan Shepherd

Information & Knowledge Manager:
Miss Heather Coupar

SPCRN Co-ordinator
Dr Kelly McGorm

Accountant:
Ms Sheevaun McIntyre

Assistant Accountant:
Mr Neil McLean

Trial Support Officer:
Ms Dorothy Aitken

Office Manager:
Mrs Glynis Omond

Administrative Assistant:
Ms Sandra Muir

St John's – Administrator:
Mrs Anne Addison

HAC/SM/approval/2c

27th June 2007

Professor Marie Fallon
Edinburgh Cancer Centre
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU

Dear Professor Fallon

MREC No:	**N/A**
CRF No:	**N/A**
LREC No:	**07/S1102/27**
R&D ID No:	**2007/W/ON/16**
Title of Research	Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain.
Protocol No/Acronym:	**N/A**

The above project has undergone an assessment of risk to NHS Lothian and review of resource and financial implications. I am satisfied that all the necessary arrangements have been set in place and that all Departments contributing to the project have been informed.

As this is a single site project involving patients and led by you as a University employee, NHS Lothian agrees to act as Co-Sponsor with University of Edinburgh.

On behalf of the Chief Executive and Medical Director, I am happy to grant management approval from NHS Lothian to allow the project to commence, subject to the approval of the appropriate Research Ethics Committee(s) having also been obtained. You should note that any substantial amendments must be notified to the relevant Research Ethics Committee and to R&D Management with approval being granted from both before the amendments are made.

Please note that under Section A, Q35, NHS Lothian provides indemnity for negligence for NHS and Honorary clinical staff for research associated with their clinical duties. It is not empowered to provide non-negligent indemnity cover for patients. NHS Lothian does not provide indemnity against negligence for healthy volunteer studies. This is the personal responsibility of both NHS and honorary employees and is usually arranged with a medical defence organisation or through the University of Edinburgh.

This letter of approval is your assurance that NHS Lothian is satisfied with your study. As Chief Investigator or local Principal Investigator, you should be fully committed to your responsibilities

"Improving health through excellence and innovation in clinical research"

within the Research Governance Framework for Health and Community Care, an extract of which is attached to this letter.

Yours sincerely

Professor Heather A Cubie
R&D Director

Enc	**Research Governance Certificate**	☑ **(to be signed and returned)**
	NRR authorisation	☑ **(to be signed and returned)**
	Tissue Policy (if applicable)	☐
	MTA (if applicable)	☐ **(to be signed and returned by the recipient of Tissue)**

Copies ***Administrators, Research Ethics Committee***
Dr Anglea Boyd, Department of Clinical Oncology, WGH

"Improving health through excellence and innovation in clinical research"

NHS LOTHIAN - UNIVERSITY HOSPITALS DIVISION

Research & Development Office, Royal Infirmary of Edinburgh

Project ID: **2007/W/ON/16**

Project Title: **Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain.**

REC Ref: **07/S1102/27**

Prinicpal Investigator: **Dr Marie Fallon**

RESEARCH GOVERNANCE FRAMEWORK (RGF) FOR HEALTH & COMMUNITY CARE

The framework is of direct relevance to all those who host, conduct, participate in, fund and manage health and community care research. The framework applies to all managers and staff, in all professional groups, irrespective of seniority.

Research Governance

- Sets standards
- Defines mechanisms to deliver standards
- Requires monitoring and assessment
- Improves research quality & safeguards the public

Responsibilities and Accountabilities of Principal Investigator (PI)

The PI must take responsibility for the conduct of the research and is accountable for this to their employer, and, through them, to the sponsor of the research and to the care organisation(s) within which the research takes place or through which participants, their organs, tissue or data are accessed. The PI must have adequate qualifications and experience to take on these responsibilities.

In brief, they must ensure that:

- The dignity, rights, safety and well being of participants are given priority at all times by the research team.
- Ethical and management approval is obtained **BEFORE** study commences.
- Care professionals involved with patients are informed of study and its protocols.
- Study complies with all legal and ethical requirements e.g. data protection, informed consent & with RGF.
- Each member of the research team is qualified to discharge their role in study and that students are adequately supervised.
- When a study involves participants under the care of a doctor, nurse or other worker for the condition in which the study relates, those care professionals are informed that their patients or users are being invited to participate and agree to retain overall responsibility for their care.
- If any information relevant to the care of a patient arises through research, the patient's care professional must be notified. Unless, the patient or the relevant research ethics committee request otherwise.
- Reporting all adverse events, including adverse drug reactions through the appropriate systems.
- Controlled trials are registered.
- Research follows an approved protocol - any proposed changes or amendments to protocol are notified to the appropriate research ethics committee, sponsor and research host.
- Findings open to critical review through accepted scientific and professional channels and disseminated promptly.
- Key role in detecting and preventing scientific misconduct, by adopting role of guarantor on published outputs.
- Arrangements in place for financial management of the study and any Intellectual Property arising from it.
- All data are stored appropriately at end of study and are available for audit.
- Procedures are in place to ensure quality data are collected, processed, analysed, stored and archived
- Progress reports are sent to sponsors promptly and are of an acceptable standard

For further information and access to the complete Research Governance document visit: -
http://www.show.scot.nhs.uk/cso

Date: 27/06/2007 1 **Signature:** ___

National Research Register - Project Details

27/06/2007

Contact Person:	Dr Marie Fallon	**Phone:**	0131 777 3518
Address:	Edinburgh Cancer Centre School of Molecular and Clinical Medicine Western General Hospital Crewe Road Edinburgh EH4 2XU	**Fax:** **EMail:**	0131 777 3520 mfallon@staffmail.ed.ac.uk

Project ID:	REC Ref:	MREC Ref;	Start Date:	End Date:
2007/W/ON/16	07/S1102/27	Not known	01/06/2007	01/06/2009

Research Title:

Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer induced bone pain.

Multi Centre: No

Lead Centre: NHS Lothian - University Hospitals Division

Research Question:

We aim to develop a tool which can be used to assess the different components of cancer-induced bone pain. This will assess the sensory aspects of pain such as response to temperature and allodynia (which means pain that is made worse by light touch). It

Outcome Measure:

The primary outcomr is validation of a tool to assess pain outcome measures.

Sample Group:

A minimum of 40 patients are required for accurate validation. All will be recruited in Edinburgh.

Study Type:

Questionnaire

Funder:	Reference:	Amount:
Wyeth (TMRC)	NS-EU-033	£284,000

Authorisation:

I authorise/have made changes and authorise/do not authorise that the above details can be supplied for inclusion in the National Research Register.

Signature: ______________ Date: 2/7/07

Please sign and return to the Research and Development Office

N. Sponsorship Approval for Main Study

ACCORD
Academic and Clinical Central Office for Research and Development

NHS Lothian

The Queen's Medical Research Institute
47 Little France Crescent, Edinburgh EH16 4TJ
Research and Development Management Suite

15 June 2007

Professor Marie Fallon
University of Edinburgh
Edinburgh Cancer Centre
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU

Dear Professor Fallon

Study Title: Pain Outcome Measures in Cancer-Induced Bone Pain
REC: 07/S1102/27

Under the requirements of the Scottish Executive Health Department's Research Governance Framework for Health and Community Care, the University of Edinburgh and NHS Lothian Health Board agree in principle to act as co-sponsors for this project. Co-sponsorship is subject to you obtaining a favourable ethical opinion and NHS Lothian R&D management approval.

As Chief Investigator, you must ensure that the study does not commence until all applicable approvals have been obtained.

Please note this letter should not be considered as NHS Lothian R&D management approval.

Following receipt of all relevant approvals, you should ensure that any amendments to the project are notified to the co-sponsors, REC, MHRA (where appropriate) and NHS Lothian R&D Office.

Yours sincerely

Tina McLelland
Research Governance Manager
Research & Development Office
NHS Lothian

Marise Bucukoglu
Associate Director
Edinburgh Clinical Trials Unit
University of Edinburgh

cc NHS R&D Office
Edinburgh Clinical Trials Unit
Dr Angela Boyd

O. *Patient Information Sheet for Main Study*

Patient Information Sheet 21 June 2007 Version 2

NHS Lothian

Study Title

Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer-induced bone pain.

Explanation of the title

This project aims to study the pain patients' experience when they have cancer in their bones. We would like to assess not only the type of pain it causes, but also the way it affects patients' feelings and ability to do things.

Introduction

Thank you for taking the time to read this. You are being asked to take part in this study because you have bone pain caused by cancer.

Before you decide to take part, please read this information sheet carefully. Ask us to explain anything that is not clear or if you would like more information about any part of the study. You are **not** obliged to take part in this study; it is your choice whether you take part or not. If you do take part, you may change your mind and leave the study **at any time**. Leaving the study or not taking part will have **no** effect on your usual medical care and you will continue to be treated by your doctor(s) as before.

Why is this study being done?

Pain caused by cancer in the bones is common and can be very troublesome for patients in a number of ways. We know that it is not only the pain itself that can cause distress. Pain can also affect people's mood, mobility and day-to-day lifestyle. In this study we are interested in finding the best way to assess a patient's pain and the other factors that go alongside this. If we can assess all these components more effectively, then we hope that this will allow us to find the most suitable treatments for you.

What the study involves for you

The study involves a combination of answering questions about your pain and how it affects your lifestyle and feelings (with questionnaires) and also tests to assess the sensation in the skin at the site of your pain (sensory tests), your walking and your daily activity. The assessment will take approximately 45 minutes.

- Initially you will be asked to fill in some questionnaires. These ask you such things as how severe your pain is and which words you would use to describe it. They also ask questions about you how the pain affects your mood and if the pain results in any fears.

- The sensory tests measure sensation in the skin at the site of people's pain. They include very briefly pressing fine plastic fibres and warm and cool rollers against your skin. Most of the tests are not uncomfortable, but if it produces a very mild discomfort, this shouldn't last for more than a few seconds.

- The assessment of your walking involves using a mat which is rolled along the floor for a length of 14 feet. The test simply involves walking along the mat, which can give us information about how your pain may affect your walking.

- The assessment of your daily activity is measured using a physical activity meter. This is a small, light box which is secured to your thigh with a sticky pad and is worn for 2 weeks at home. It should not cause any discomfort and will not interfere with your day-to-day life.

We are aiming to complete at least one full 45 minute assessment of your pain. However, with your agreement we would like to perform this assessment again. We would plan to see you approximately 6 weeks after the first assessment and then in approximately 3 to 4 months. These extra assessments will allow us to see if your pain has improved over time with the treatment provided by your own doctor. Once these tests are complete, your involvement in the study will have finished.

The study doctor can remove you from the study, without your consent, for any reason. Possible reasons for doing so may include a change in your medical condition which prevents continued participation in the study, if you need to receive any therapy that prevents ongoing study participation or termination of the study.

Where and when will the study take place?

If you agree to take part in the study, we will arrange a time to see you in the outpatient department of the Edinburgh Cancer Centre at the Western General Hospital. It is important that you have sufficient time to consider taking part in this study and that it causes you as little inconvenience as possible. The assessments can be done at a time during the day that suits you. If this visit is for the sole purposes of the study, we will pay for this journey.

Consent to the study

If you do decide to take part, you will be asked to sign a consent form, agreeing to the provisions of the information sheet. You will then be given a copy of the signed consent form. Your own hospital doctors and nurses are fully aware of the study and would be happy for you to take part if you wish to do so.

Patient confidentiality

Any information that you give before or during the study will be kept in strict confidence. Your medical records may be read by the study doctor or nurse, but care will be taken so that you cannot be identified when we write reports of the study. Your full name will not be used on study documents; you will be referred to only by your initials and an identity number. We will contact your own G.P. to tell them about you taking part in the study. We will also tell them and your hospital doctors if you have pain that would require changes in your treatment. Occasionally research projects are checked by regulatory authorities to ensure that research is being done properly. In this situation, these authorities may need to look at your medical notes.

The possible disadvantages to you

The main disadvantage of taking part will be the additional time required to do the assessments and this may mean extra visits to the outpatient department over and above your usual appointments.

The possible benefits to you

The study will provide a detailed assessment of your pain and how it is affecting your lifestyle and how you feel. If we discover that your pain is causing problems we may either start appropriate treatment or will inform your own doctors so that changes can be made in your medication. The information you provide may help us to assess bone pain more quickly and fully, and so help others be treated more effectively in the future.

Who has reviewed the study?

This study has been looked at by a group of doctors, nurses and non-medical people whose job it is to check that any research that is being done is both valuable and safe.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed appropriately using the NHS Complaints Procedure.

What will happen with the results of the study?

Once the study is complete, if you are in agreement and would like to be updated, we will inform you verbally of the results of the research.

Who is organising and funding the study?

The study is being funded by the Scottish Translational Medicine Research Collaboration (TMRC). This Collaboration comprises four of Scotland's leading universities working with Wyeth Pharmaceutical Co, Scottish Enterprise and NHS Scotland. The study is being organised by members of the Lothian Chronic Pain Service and the Edinburgh Pain Group at the Western General Hospital.

Who can I contact for further information?

If you would like any further information about this study you are welcome to contact:

Dr. Angela Boyd, Clinical Research Fellow, Edinburgh Cancer Centre, WGH
Tel: (0131) 537 1000 or (0131) 777 3529

Dr. Lesley Colvin, Consultant Anaesthetist and Senior Lecturer in Pain Medicine, WGH
Tel: (0131) 537 1000

Prof. Marie Fallon, Consultant in Palliative Medicine, WGH
Tel: (0131) 537 1000

If you would like to speak with someone who is independent of this study, please contact:

Dr. Ivan Marples, Consultant in Pain Medicine and Anaesthetics, Dept. of Clinical Neurosciences, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU.
Tel: (0131) 537 1659

Thank you for taking the time to read this information sheet. We hope that you do decide to take part in the study, but we reassure you that your care will not be affected in any way if you decide not to take part.

P. *Consent Form for Main Study*

Patient Identification Number for this trial: Date:

NHS
Lothian

CONSENT FORM

11 May 2007 Version 1

Title of Project:

Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer-induced bone pain.

Name of researchers:
Dr. Angela Boyd, Clinical Research Fellow
Dr. Lesley Colvin, Consultant Anaesthetist
Prof. Marie Fallon, Consultant in Palliative Medicine

6. I confirm that I have read and understand the Patient Information Sheet dated ___/___/___ for the above study and have had the opportunity to ask questions.

7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

8. I understand that sections of any of my medical notes may be looked at by responsible individuals or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

9. I agree to take part in all the assessments as described in the Patient Information Sheet.

10. I agree to allow my hospital doctor and G.P to be informed of my participation in the study and for them to be contacted additionally if it may improve my management.

11. I agree to be contacted by one of the researchers once the study is complete to be updated on the results of the study.

________________________ ____________ ________________________
Name of Patient Date Signature

________________________ ____________ ________________________
Name of Person Taking Consent (Researcher) Date Signature

One copy for patient, one for researcher & one to be kept with hospital notes

Q. G.P. Information Sheet for Main Study

Palliative Care Research Team
Western General Hospital, Edinburgh

11 May 2007 Version 1

NHS Lothian

CONFIDENTIAL

Dear ________________________________ Date: __________

Patient's name: ________________________ DOB: __________
Address: ________________________
____

Study Title: **Development of a systematic approach to assess the sensory, cognitive, affective and functional components of cancer-induced bone pain.**

This letter is to inform you that the above named patient has consented to participate in a clinical trial being undertaken by members of the Edinburgh Pain Research Group at the Western General Hospital. The Scottish Translational Medicine Research Collaboration (TMRC) is funding the study.

Cancer-induced bone pain (CIBP) is a major clinical problem, is common in cancer patients and can be severely debilitating. The aim of this study is to develop a validated tool to assess the different components of CIBP - sensory, cognitive, affective and functional. Your patient will attend the Best Supportive Care Clinic and the additional assessments required for the trial will be done during the visit. If this is not convenient for him / her, an alternative time will be arranged and transport provided if necessary. The additional assessment should take up to 45 minutes to complete and involves Quantitative Sensory Testing, gait and activity assessment, and completion of validated questionnaires.

We plan to review your patient again, with their agreement, approximately 6 weeks later and then at approximately 3 to 4 months at the Best Supportive Care Clinic and repeat the above assessments on each visit. If your patient has symptoms that suggest a change of treatment is indicated, then we will be in contact to discuss this with you.

If you have any questions or would like any further information about this study you are welcome to contact a member of the research team:

- **Dr. Angela Boyd, Clinical Research Fellow with the Palliative Care Team at the Edinburgh Cancer Centre, Western General Hospital.**
  Tel: (0131) 537 1000 or (0131) 777 3529
- Dr. Lesley Colvin, Consultant Anaesthetist and Senior Lecturer in Pain Medicine at the Western General Hospital. Tel: (0131) 537 1000
- Prof. Marie Fallon, Consultant in Palliative Medicine at the Western General Hospital. Tel: (0131) 537 1000 or (0131) 777 3518

Yours sincerely,

Prof. / Dr. ________________________

R. Letter of Response to Patients for Main Study

Edinburgh Cancer Centre
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU

30th November 2009

Dear ________________________,

I am writing to thank you for participating in the bone pain study and to update you of the findings.

The activity meters showed us that bone pain made it harder for some people to be as active. When pain improved after radiotherapy, people felt less anxious and depressed and they were less fearful about their pain. We also found that sensation in the skin overlying the painful area went back to normal in some people when their bone pain improved. Increased or reduced sensitivity to cold in the skin was associated with improved pain after radiotherapy. This will be examined in a larger study and has given us a very important pointer to a potential way of identifying in advance those patients most likely to get good pain relief from radiotherapy.

The study has been really beneficial. It has helped us to understand how bone pain affects daily life. This means that we can try to improve bone pain and the treatment for other patients in the future. Many thanks again.

Yours sincerely,

Dr. Angela Scott (Boyd)

Specialist Registrar in Medical Oncology

S. Can We Identify the Mechanisms of Cancer-Induced Bone Pain with Quantitative Sensory Testing? (Oral Presentation)

Palliative Medicine 2008; **22**: 399–558

EAPC Abstracts

86 Oral Presentation

Title: Can We Identify the Mechanisms of Cancer-Induced Bone Pain with Quantitative Sensory Testing?
Authors: Angela C Boyd; Sandra McConnell; Siobhan Duncan; Barry J A Laird; Lesley Colvin & Marie T Fallon
Background: Cancer-induced bone pain (CIBP) is associated with increased morbidity, anxiety and depression and reduced performance and quality of life. It remains a considerable therapeutic challenge that has been neglected in research. Clinical characterisation will aid understanding of the mechanisms of CIBP providing a comprehensive pain assessment and application of targeted treatment. Aim: to characterise the different components of CIBP using Quantitative Sensory Testing (QST) as a measure of altered sensory processing.
Methods: 45 patients with CIBP were analysed. They completed the Brief Pain Inventory (BPI) and a QST assessment of the painful area plus an appropriate control site. Standard descriptive statistics were used to calculate the demographic, clinical measures and questionnaire results.
Results: The sample comprised 20 men and 25 women (average age of 65.6 years, range 41-83 years). Median scores for "pain right now", "average pain" and "worst pain" were 4, 5 and 8 out of 10 respectively. Abnormal sensation was elicited with brush testing in 24 (53.3%); of these 15 had increased and 9 reduced sensitivity. 16 of the 45 patients (35.6%) had dynamic mechanical allodynia. Mechanical responses to von Frey hairs were significantly altered over the affected area for both detection and pain thresholds. 26 patients (57.8%) had increased warm sensitivity; 19 patients rated this as painful. 5 patients (11.1%) had reduced warm sensitivity. 24 patients (53.3%) had increased and 2 (4.4%) reduced cool sensitivity; 16 patients rated this as painful. 19 patients (42.2%) had increased sensation to both warm and cool. Only 11 patients (24.4%) had entirely normal thermal sensation.
Conclusions: Altered mechanical and thermal sensitivity is present in a significant proportion of patients with CIBP, indicating unique changes in the underlying neurobiology that have not previously been demonstrated clinically. This clinical evidence of underlying pathways can be used to start developing targeted interventions.

T. Sensory Characteristics of Cancer-Induced Bone Pain: Response to Palliative Radiotherapy (Poster)

Sensory Characteristics of Cancer-Induced Bone Pain: Response to Palliative Radiotherapy

Abstract no: 3386

[a]Boyd A; [a]McConnell S; [a]Laird B; [b]Colvin L; [a]Fallon M

[a]Edinburgh Cancer Research Centre / [b]Dept of Anaesthesia, Critical Care & Pain Medicine, Western General Hospital, Edinburgh, EH4 2XR

Introduction

Bone is the third most common site for metastatic disease, but is the commonest cause of pain [1]. Cancer-induced bone pain (CIBP) is associated with increased morbidity, anxiety and depression and reduced performance and quality of life. It remains a considerable therapeutic challenge that has been neglected in research.

Radiotherapy (XRT) is the gold standard treatment for CIBP. However only 50% patients achieve adequate pain relief [2,3].

Currently there are no established biomarkers which predict response to treatment. Lack of full understanding of the underlying pathophysiology hampers development of novel targeted treatment. It is a unique pain that differs from both inflammatory and neuropathic pain [4].

Aim

The aim of this work was to:
- characterise the sensory aspects of CIBP
- explore the sensory changes in response to palliative XRT

Method

Patients with CIBP scheduled to receive palliative XRT underwent assessment prior to and 4-6 weeks after treatment.

Assessment comprised:
- Short form Brief Pain Inventory (BPI)
- Quantitative Sensory Testing (QST)

QST included assessment of dynamic and thermal allodynia using brush testing and warm/cool rollers, and measurement of the area of abnormal sensation.

Standard descriptive statistics were used to calculate the demographic, clinical measures and questionnaire results.

Results

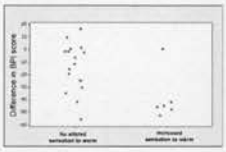
23 patients (13 male, 10 female), median age 73 (range 33 to 83) years, receiving XRT for CIBP underwent both pre and post treatment assessment. Breast (35%) and prostate (39%) were the most frequent primary tumour sites. We have previously shown that worst and total BPI scores reduced from a mean of 7.5 to 5 and from 68.4 to 47.4 respectively after XRT. Interference score also improved from a mean of 31.7 to 18.3 after treatment.

Dynamic Mechanical Allodynia
Prior to treatment 8 (35%) of patients had abnormal sensitivity to calibrated brush. This area entirely resolved in 3 patients and reduced in size in 4 patients after XRT. Affected area improved from a mean of 17646mm² to 1623mm² (n=7). Dynamic allodynia resolved in 2 patients.

Thermal Thresholds
Abnormal sensitivity to warm stimulus (40°C)was seen in 14 patients, of which 6 cases resolved to normal after XRT. 10 patients had altered sensitivity to cool (25°C), of which 6 also normalised after treatment.

Differences were noted between those who had normalisation of abnormal warm sensation (warm responders,n=6) in comparison with the other patients (n=17):

- "Warm responders" had higher baseline pain scores, with pre-treatment mean BPI interference scores of 43.8 vs 27.4 and total BPI scores of 79.7 vs 64.5.
- Improvements in scores after XRT in warm responders were larger than in other patients. BPI interference improved by a mean of 25.5 vs 9.1 and total BPI by 38.9 vs 14.7 when comparing warm responders and all others (median difference of 33.5 in total BPI, **p=0.027**).



- Proportionally more warm responders (50%) had reduced size of abnormal area with brush after XRT vs 23.5% of other patients. Similarly more warm responders (50%) had resolution of hyperaesthesia to pinprick after XRT vs 17.6% of other patients.
- If we classify those with an analgesic response to XRT as having a 30% improvement in total BPI, 83.3% of warm responders compared with 47.1% of other patients gained an analgesic benefit.

Conclusion

There is a suggestion that patients with CIBP with resolution of altered sensitivity to warm thermal stimulus after XRT have larger reductions in pain scores, increased likelihood of resolution of sensitivity to pinprick and improvement in size of altered area to brush than those without warm sensitivity resolution.

Use of the BPI and QST to assess CIBP demonstrates unique changes in the underlying neurobiology and provides a simple tool which may be useful as a potential biomarker to predict response to palliative XRT. Further research is required to assess the applicability of these findings in the clinical setting.

References

1. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997;69:1-18.
2. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. Cancer 1982; 50: 893-899.
3. McQuay H, Collins S, Carroll D, Moore R. Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev 2000; CD001793.
4. Urch C. The pathophysiology of cancer-induced bone pain: current understanding. Palliative Medicine 2004; 18:267-274.

U. Cancer-Induced Bone Pain: Objective Functional Assessment in Relation to Palliative Radiotherapy (Poster)

Cancer-Induced Bone Pain: Objective Functional Assessment in Relation to Palliative Radiotherapy

NHS Lothian

Poster Number: A72

[a]Boyd A; [a]Laird B; [b]Fleetwood-Walker S; [c]Mitchell R; [d]Wan H; [a]Fallon M; [e]Colvin L

[a]Edinburgh Cancer Research Centre / [e]Dept of Anaesthesia, Critical Care & Pain Medicine, Western General Hospital; [b]Veterinary Biomedical Sciences / [c]Centre for Integrative Physiology, University of Edinburgh; [d]Wyeth Research, Collegeville, USA

Introduction

Bone is the third most common site for metastatic disease, but is the commonest cause of pain [1]. Cancer-induced bone pain (CIBP) is associated with increased morbidity, anxiety and depression and reduced performance and quality of life. It remains a considerable therapeutic challenge that has been neglected in research.

To optimise pain control and objectively measure response to radiotherapy (XRT), it is important to assess the multi-dimensional components of CIBP:sensory, affective, cognitive and functional.

There are currently no known biomarkers predictive of response to XRT.

Aim

The aim of this work was to:
- Use a refined functional assessment to measure the effect of radiotherapy on these different components of CIBP.
- Consider whether this can be utilised as a clinical predictor of response to treatment.

Method

After ethical approval and written informed consent, patients with CIBP scheduled to receive palliative XRT were recruited from the Edinburgh Cancer Centre. A comprehensive pain assessment tool was completed at study entry (pre-XRT), 6-8 weeks and 3-4 months after XRT.

Assessment included:

- Short form Brief Pain Inventory (BPI)
- Gait assessment with GAITRite electronic walkway
  - a 14-foot computer based instrumented walkway that measures spatial and temporal gait characteristics
- Functional activity assessment with activPAL™ physical activity meter
  - records step number and cadence for each period of walking
  - classifies individual's free living activity into periods spent lying, standing & walking
  - can estimate daily energy expenditure & provides a "real-life" measure of functional impairment

Standard descriptive statistics were used to calculate the demographic, clinical measures and questionnaire results.

References

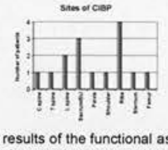
1. Mercadante S. Malignant bone pain: pathophysiology and treatment. Pain 1997;69:1-18.

Acknowledgements

This work was supported by an award from the Translational Medicine Research Collaboration

Results

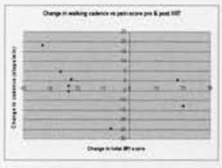
15 patients completed the baseline assessment, of which 6 were male and 9 female, with a median age of 66 (range 44-88) years. Diagnoses included breast (53%), prostate (33%) and lung cancer (13%).



Most common site of CIBP were vertebral and rib metastases.

The results of the functional assessments of the first 8 patients with post-radiotherapy data are presented. Of these 8 patients, 5 (62%) responded to radiotherapy for pain control. Comparisons between these "responders" and "non-responders" have been examined. All reported values are means (±unbiased standard deviation).

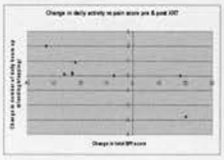
Worst and total Brief Pain Inventory scores improved by 3.2(±2.8) and 25.4(±4.5) respectively in responders; worsened by 1.3(±1.2) and 10.3(±15.0) in non-responders.

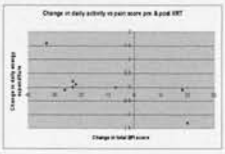


Improvements in pain were mirrored by improvements in gait, with velocity faster by 4.5(±13.5)cm/sec in responders; slower by 13.9(±16.1) cm/sec in non-responders.

Cadence and functional ambulatory score showed similar trends.

Responders stood/walked for longer (increased 0.7±0.8 hours/day) after treatment; non-responders reduced activity duration (decreased 0.9±1.6 hours/day).





Calculated energy expenditure improved in responders (by 0.4±0.7 MET/hr); worsened in non-responders (by 0.5±0.7MET/hr).

Conclusion

- Refined objective functional assessments give consistently agree with subjective analgesic responses to the gold standard treatment of radiotherapy for cancer-induced bone pain.
- This may provide a new technique to assess response to both standard treatments and novel analgesic therapies.
- Discovery of a biomarker to predict response to radiotherapy for malignant bone pain will allow targeted individualised care with potential benefits for both patients and health economics.
- Further research is required to assess the applicability of these findings in the clinical setting.

V. Functional assessment predicts ability to complete trial follow up in cancer-induced bone pain (Abstract).

Background: Cancer-induced bone pain (CIBP) results in reduced physical activity with poor quality of life. Objective evidence of the functional impact of CIBP is lacking. **Aim:** to measure function in patients with CIBP before and 6-8 weeks after radiotherapy (XRT).

Methods: ActivPAL physical activity meters were used to record function. Wilcoxon signed rank test analysed the differences before and after XRT. Mann-Whitney test compared patients completing two assessments and those who dropped out of the study. Multivariate analysis looked for independent predictors of inability to complete two assessments.

Results: After ethical approval, 59 patients completed a baseline assessment (24 male (41%) and 35 female (59%), median (range) age of 63 (38-88) years). Primary sites included breast (51%), prostate (25%) and lung (15%) with spine the most frequent site of CIBP. Forty-two patients (71%) completed a second assessment after XRT. Failure to attend was primarily due to death or disease progression. Statistically significant differences were seen between those completing one or two assessments (Table 1). Energy expenditure was independently predictive of inability to complete the study (p=0.002). No statistically significant differences were seen after XRT.

Pre-XRT Activity Meter Results	Completed 2 Visits (n=42)		Dropped Out of Study (n=17)		P Value
	Median	Range	Median	Range	
Daily hours sitting/lying	19.7	16.5-23.8	22.2	17.2-23.73	0.0082
Daily hours standing	3.3	0.1-5.5	1.5	0.24-5.3	0.0141
Daily hours stepping	0.9	0.03-2.3	0.3	0.02-2.1	0.0037
Energy expenditure (MET/hr)	32.1	30.2-35.3	30.7	30.1-34.5	0.0019
Daily number of steps	4223	92-12225	1094	71-9636	0.0025

Conclusions: Identification, recruitment, enrolment and retention of patients with advanced cancer in clinical trials are difficult. Objective functional assessment may have clinical utility in helping decide who might be suitable for study inclusion or fitness to receive a specific treatment. The study was funded by the Translational Medicine Research Collaboration.

W. The psychological benefits of radiotherapy for cancer-induced bone pain (Abstract).

Background: Cancer-induced bone pain (CIBP) is associated with increased morbidity, anxiety, depression and reduced quality of life. Radiotherapy (XRT) is the gold standard treatment, but its effects on the psychological component of pain are not fully characterised. **Aim:** to assess the cognitive and affective components of CIBP before and after XRT.

Methods: The Brief Pain Inventory (BPI), McGill Pain Questionnaire (MPQ), Hospital Anxiety and Depression Scale (HADS), Fear and Avoidance of Pain Scale (FAPS) and Pain Catastrophizing Scale (PCS) were completed before and 6-8 weeks after XRT for CIBP. Analgesic response was defined as a reduction in worst pain score of $\geq$ 30% at the irradiated site. Wilcoxon signed rank test compared differences before and after XRT. Mann Whitney test compared responders and non-responders.

Results: After ethical approval, 42 patients completed an assessment pre and post XRT (16 male (38%) and 26 female (62%), median (range) age of 65.5 (38-88) years). The most common primary sites were breast (52%), prostate (29%) and lung (12%) with spine the most frequent site of CIBP. 29 patients (69%) responded to XRT. Table 1 shows the median (range) questionnaire results. Anxiety, depression, fear avoidance and catastrophizing improved significantly in responders, but not in non-responders.

Questionnaire Results	Responders (n=29)			Non-responders (n=13)		
	Pre XRT	Post XRT	P value	Pre XRT	Post XRT	P value
BPI Worst Pain	7 (2-10)	2 (0-7)	<0.001	6 (1-8)	5 (1-10)	0.64
Total BPI	49 (12-94)	6 (0-64)	<0.001	45 (8-98)	30 (2-72)	0.06
Total MPQ	13 (1-33)	2 (0-18)	<0.001	10 (2-25)	7 (0-22)	0.82
HADS Anxiety	5 (0-14)	3 (0-14)	0.025	4 (1-17)	3 (0-18)	0.29
HADS Depression	5 (1-14)	3 (1-15)	0.018	5 (0-14)	5 (0-12)	1.00
Total FAPS	60 (4-111)	22 (0-101)	<0.001	62 (5-109)	49 (0-111)	0.68
Total PCS	7 (0-42)	2 (0-38)	0.003	5 (0-34)	3 (0-35)	0.54

Conclusions: Improvements in pain with XRT were mirrored by psychological benefits. Addressing the multi-dimensional components of CIBP has the potential to improve quality of life for patients living with bony disease.

X. Use of thermal sensation as a biomarker of response to palliative radiotherapy for cancer-induced bone pain (Abstract).

Background: Radiotherapy (XRT) is the gold standard treatment for cancer-induced bone pain (CIBP), but not all patients achieve adequate analgesia. The aim of this study was to identify predictors of response to XRT for CIBP, as currently no clinical biomarkers of response are known.

Methods: The Brief Pain Inventory (BPI) and Quantitative Sensory Testing (QST) were completed before and 6-8 weeks after XRT for CIBP. Using warm (40°C) and cool (25°C) rollers in the CIBP and control sites, thermal sensation was tested. Analgesic response was defined as a reduction in BPI worst pain score of ≥30% at the CIBP site. Mann-Whitney test compared responders and non-responders and those with normal and abnormal sensation. Multivariate regression analysis examined potential predictors of response to XRT.

Results: 42 patients were assessed pre and post XRT (16 male (38%), median (range) age 65.5 (38-88) years). Primary sites included breast (52%), prostate (29%) and lung (12%) with spine the most common site of CIBP. 29 patients (69%) responded to XRT. In responders, the number of patients with normal cool sensation increased from 3 (10%) pre XRT to 13 (45%) after XRT and fell in non-responders from 5 (38%) to 4 (31%). Number of patients with normal warm sensation increased from 6 (21%) to 14 (48%) in responders and decreased from 6 (46%) to 5 (38%) in non-responders. Median (range) reduction in worst pain (0-10 scale) in those with altered warm sensation was 3 (-2-10) vs 1.5 (-2-5) in those with normal sensation ($p=0.02$). In those with altered cool sensation before XRT, worst pain score improved by 3 (-2-10) vs 1.5 (-2-5) in those with normal sensation ($p=0.03$). For patients with altered warm and cool sensation the median (range) improvement was 3.5 (-2-10) vs 2 (-2-5); $p=0.01$. Patients with reduced sensation to cool at baseline were more likely to respond to XRT (odds ratio 6.67, 95% CI 0.99-45). Abnormal cool sensation was independently predictive of response ($p=0.03$).

Conclusions: Predicting analgesic response to XRT would enable individualised care, avoiding unnecessary treatment in a frail population with limited life expectancy. Thermal assessment could be incorporated easily into practice and warrants further investigation.

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